SENSORIMOTOR REORGANIZATION
IN RELATION TO HAND FUNCTION
FOLLOWING UNILATERAL BRAIN LESIONS

Mominul Islam
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TO MY PARENTS

"Life is like a box of chocolates. You never know what you're gonna get."

- Forrest Gump
ABSTRACT

Most activities of daily living require skillful use of our hands. Whatever the complexity of the task, our ability to perform any motor function largely relies on the integrity of the widely distributed corticomotor network. Damage to the central nervous system at any stage our life results in functional limitations to various extents. How the body responds in order to recover from such injuries will vary depending on the time, location and severity of the brain lesions. This is particularly true of children with early brain lesions, since an immature nervous system is known to have superior compensatory capabilities. Irrespective of the severity of impairment and the level of recovery, decreased ability in terms of effective hand function has a huge negative impact on the quality of day-to-day activities and personal wellbeing.

The overall aim of this thesis is to investigate the relationship between hand function and different types of unilateral brain lesions from the perspective of development, training outcomes and clinical measurements.

We have investigated children with unilateral cerebral palsy (CP) in Studies I, II and III. The aim of the Study I was to investigate the relationship between brain lesion characteristics, organization of corticomotor-projection and hand function. Results showed a wide variation in hand function and the children with ipsilateral projection pattern showed lower ability than those with contra lateral pattern. We also found that corticomotor-projection pattern can be influenced by lesion extent and location but not lesion type. We investigated these issues further in relation to the outcome of intensive training in Study II. In this study, we were able to show that children with unilateral CP were able to improve after intensive training, independent of their lesion characteristics and (re)organization of motor projection patterns. The results from Study III showed that, when performing asymmetric bimanual tasks, children with unilateral CP have impaired temporal and force coordination but are still able to complete these tasks through an alternative strategy compared with typically developing children. Impairment was greater when the non-paretic hand served as the holding hand. Interestingly, the ability of the non-paretic hand was affected by the ability of the paretic hand.

Study IV was designed to develop and validate a method to quantitatively measure “spasticity”, which is a very common clinical symptom after an injury of the central nervous system. While investigating a group of adults with unilateral stroke, our results validated a biomechanical model that could separate and measure neural contribution in the generation of spasticity in the hand. The findings from this study have significant implications in relation to measuring spasticity directly in clinical settings.

Overall, this thesis holds direct clinical implication through our efforts to describe and assess hand function after unilateral brain lesions in both children and adults. With combined use of neurophysiology and neuroimaging methods, we could better describe both unimanual and bimanual abilities in children with reorganized corticomotor-projection and also could indicate the potentials to improve after intensive training. A quantifiable measurement of spasticity is possible to be used in clinical settings.

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LIST OF PUBLICATIONS


II. Islam M, Nordstrand L, Holmström L, Kits A, Persson JKE, Eliasson AC
   Improvement following constraint-induced movement therapy (CIMT) in relation to corticomotor-projection patterns and brain lesion characteristics in unilateral cerebral palsy (submitted).

III. Islam M, Gordon AM, Sköld A, Forssberg H, Eliasson AC

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<tbody>
<tr>
<td>AHA</td>
<td>Assisting hand assessment</td>
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<td>AS</td>
<td>Ashworth scale</td>
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<td>B&amp;B test</td>
<td>Box and blocks test</td>
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<td>BG</td>
<td>Basal ganglia</td>
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<td>CIMT</td>
<td>Constraint-induced movement therapy</td>
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<td>CP</td>
<td>Cerebral palsy</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
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<td>EC</td>
<td>Elasticity component</td>
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<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GF</td>
<td>Grip force</td>
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<td>GMFCS</td>
<td>Gross motor function classification system</td>
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<td>IC</td>
<td>Inertia component</td>
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<td>LF</td>
<td>Load force</td>
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<td>M1</td>
<td>Primary motor area</td>
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<td>MACS</td>
<td>Manual ability classification system</td>
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<td>MEG</td>
<td>Magnetic encephalography</td>
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<td>MEP</td>
<td>Motor evoked potential</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>mV</td>
<td>Mill volts</td>
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<tr>
<td>N</td>
<td>Newton</td>
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<tr>
<td>NC</td>
<td>Neural component</td>
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<tr>
<td>nTMS</td>
<td>Navigated transcranial magnetic stimulation</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PMR</td>
<td>Passive movement resistance</td>
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<td>SEP</td>
<td>Sensory evoked potential</td>
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<td>T</td>
<td>Tesla</td>
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<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
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<tr>
<td>UL-MAS</td>
<td>Upper limb-motor assessment scale</td>
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<tr>
<td>VC</td>
<td>Viscosity component</td>
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<tr>
<td>WMDI</td>
<td>White matter damage of immaturity</td>
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1 INTRODUCTION

In most day-to-day activities we make skillful use of our hands, without being fully aware of the complexities of the tasks. Even a simple motor activity is driven by a series of complex neurological events. One good example to elaborate that would be the process of pouring water from a jar into a glass. To begin with the task, when reaching out to lift the glass, we must first mentally perceive the shape and the weight of the glass, plan which groups of muscles should be activated, decide how much force to generate to lift the glass and the jar, compile all these decisions and encode them to initiate a motor command to activate the muscles and achieve proper coordination between two hands for holding and pouring. Simultaneously, the motor commands need to be adjusted according to the sensory information received while performing the task. This means that the whole process is a combination of sensory input and motor outputs distributed over a wide circuit between the central and peripheral nervous system. A disruption anywhere in the sensory-motor circuit could result in the whole task breaking down. Thus, if the function of one hand is impaired, we commonly encounter limitations in performing even a simple bimanual task that requires the use of two hands together.

In the case of an injury to the central nervous system, hand function is frequently impaired. Common clinical features include slowness, weakness, sensory disturbances, lack of coordination between two hands, impaired force generation and spasticity of hand muscles. The ability to recover from such impairments could be different in the case of children compared to adults, since the developing brain is more able to compensate for these injuries, for example in children with unilateral cerebral palsy (CP). However, some symptoms of unilateral brain lesion, such as spasticity, are common both in adults with stroke and in children with cerebral palsy. Continuous efforts are being made by researchers and clinicians to understand which mechanisms drive functional impairments and subsequent recovery, so that we can develop effective clinical strategies to overcome functional limitations and improve quality of life.

Thus, in this thesis, our overall aim is to investigate hand function in both children and adults, from the perspective of development, training outcomes and clinical measurements, particularly in respect to unilateral brain lesions.
1.1 CEREBRAL PALSY

1.1.1 Definition and demography

Cerebral palsy (CP) is a disorder of the developing brain. It was first described in 1843 by an orthopedic surgeon “William John Little” and was known as “Little’s disease”. The term “cerebral palsy” was introduced in 1889 by Sir William Osler. The most recent definition of cerebral palsy was proposed by Rosenbaum et al. (Rosenbaum 2007):

“Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitations, that are attributed to non-progressive 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 behavior; by epilepsy, and by secondary musculoskeletal problems.”

A recent population-based study in Sweden reports that the prevalence of cerebral palsy is 2.18 per 1000 live births (Himmelmann et al. 2010). About one third of the children with CP present with unilateral spastic type, half with bilateral spastic type and the remaining with less common types, such as dyskinetic and ataxic CP (Himmelmann et al. 2011). CP has a higher prevalence in children born preterm (Himpens et al. 2008). Gestational age-specific prevalence for <28 gestational weeks is about 56 per 1000 live births (Himmelmann et al. 2010).

The Surveillance of Cerebral Palsy in Europe (SCPE 2005) have classified children with spastic CP as, unilateral or bilateral CP. Two major classification systems are used for assessing gross motor and bimanual functions in children with CP, i.e., (a) Gross Motor Classification System (GMFCS) (Palisano et al. 1997; Rosenbaum et al. 2008) and (b) Manual Ability Classification System (MACS) (Eliasson et al. 2006; Ohrvall and Eliasson 2009).

1.1.2 Etiology and pathophysiology

CP is the result of non-progressive disturbances of the developing fetal brain and up to two years of age (Rosenbaum 2007). The lesions are not always caused by a single factor, but various interacting factors in combination contribute to the pathology in the developing brain. The role of gestational age at birth, e.g., born pre-term, is frequently indicated as a crucial risk factor (Krageloh-Mann and Horber 2007; Volpe 2009; Himmelmann et al. 2011;
Skiöld et al. 2012). The maturity of the central nervous system at the time of injury, together with the location and extent of the lesions, contribute significantly to the clinico-pathological outcomes. Several antenatal factors have also been discussed as risk factors, such as maternal infection, antibiotic intake during the pregnancy, multiple pregnancy (twin/triplets) and assisted conception. Bax et al. reported that 29.6% of the mothers whose children were subsequently diagnosed with CP had significant infection (excluding cases of common colds, coughs, etc.) during the pregnancy (Bax et al. 2006). Incidence of cerebral palsy is higher in preterm males than females (Wu et al. 2006; Himmelmann et al. 2010). Moreover, the role of perinatal events such as birth asphyxia and perinatal stroke is also crucial in pathological outcomes.

The pathological features of brain lesions in preterm infants are heterogeneous, yet one predominant finding in preterm type brain injuries is periventricular leucomalacia (PVL), which is a form of hypoxic-ischemic brain damage (Kulak et al. 2008). The pathogenesis behind PVL in preterm infants has been attributed to the incomplete development of the vascular supply to the cerebral white matter before 32 weeks in the gestational period. Moreover, during this period the pre-oligodendrocytes at the periventricular region remain highly susceptible to any ischemic injury and resulting changes in oxygen saturation in the tissue, leading to pre-oligodendroocyte destruction and cerebral leuco-encephalopathy (Blumenthal 2004; Van den Broeck et al. 2008).

1.1.3 Hand function in unilateral CP

In unilateral CP, the impairment of upper limb functions is predominant on one side. The most common clinical features in the paretic extremity include slowness, abnormal muscle tone, decreased strength and coordination difficulties, which occur to a varying extent (Uvebrant 1988). Many children also have impaired sensibility (Krumlinde-Sundholm and Eliasson 2002) and mirror movements (Kuhtz-Buschbeck et al. 2000). Furthermore, children with hemiplegia also show difficulty in the timing and coordination of reaching movements (Utley and Sugden 1998), grasping (Forssberg et al. 1999; Gordon and Duff 1999; Duff and Gordon 2003), movement planning (Steenbergen et al. 1998), and a deficient capacity to modulate postural adjustments during reaching (Hadders-Algra 2001). However, unilateral impairments do not have too much impact on unimanual activities, e.g., brushing teeth, combing hair, since they can be performed with the non-paretic hand. But very many common activities in daily life would actually require them to use both hands together. Tasks where two hands need to perform opposite force coordination, e.g., pouring a glass of water, buttoning clothes, or tying shoes (Sköld et al.
2004), are even more difficult to perform. However, only a few studies have looked at grip force coordination during bimanual tasks in children with unilateral CP (Sugden and Utley 1995; Gordon et al. 2006a; Steenbergen et al. 2008). While investigating bimanual reaching and grasping using a speed constraint, Utley and Sugden (1998) suggested that in children with unilateral CP, bimanual movement can assist the less-impaired limb to guide the more paretic side to perform better (Utley and Sugden 1998). Steenbergen et al. (1996) reported that the difference in impairments between the paretic and non-paretic hands was minimized during a symmetrical bimanual task involving grasping and releasing with both hands at the same time (Steenbergen et al. 1996). Hung and co-authors have indeed investigated asymmetric hand function, using a drawer-opening task. In their experiments, the children were asked to reach forward and open a drawer with one hand and then activate a light switch inside the drawer with the contralateral hand under different speed and hand constraints. They found children with unilateral CP to be slower and less coordinated (Hung et al. 2004; Hung et al. 2010). All these studies suggest that children with unilateral CP have the ability to coordinate their bimanual movements through compensation, as long as the accuracy demands or task complexities were not too extensive. In contrast to the examples above, little is known about bimanual coordination in unilateral CP during complex asymmetrical tasks, when the hands are required to perform opposite force coordination.

Moreover, cerebral palsy is a heterogeneous disorder and can also be present with other systemic problems, such as cognitive impairment (Chong et al. 2012) and/or visual disturbance (Himmelmann et al. 2006), which might have a further negative impact on hand functions. Tasks which would require specific hand-eye coordination are likely affected by decreased visual acuity. With impaired cognition, children will not only have an impaired ability to understand instructions of the therapy but also will have lack of motivation to execute the tasks. So, these factors are also crucial when it comes to participating in various rehabilitative measures.

**Mirror movements and hand function**

The term “mirror movements” (MM) can be described as involuntary movements that occur in the homologous muscles in a limb, opposite to the limb performing the voluntary movements (Connolly and Stratton 1968; Woods and Teuber 1978). This may be a normal feature of motor development, but in typically developing children MM gradually disappear by the first decade of life (Connolly and Stratton 1968; Lazarus and Todor 1987). Children with
hemiplegia, particularly those with greater severity, can demonstrate MM (Carr et al. 1993; Kuhtz-Buschbeck et al. 2000). Transcranial magnetic stimulation (TMS) studies (Maegaki et al. 2002; Staudt et al. 2002) and functional imaging studies (Vandermeeren et al. 2003a) have suggested links between mirror movements in children with unilateral brain lesions, ipsilateral corticomotor-projections and activation of ipsilateral unaffected hemisphere. Possible reduction of transcallosal inhibitory activity from the affected hemisphere might also contribute in bilateral activation of both hemispheres during and unimanual task and result in mirror movements.

Intensity of MM is clinically assessed with subjective ratings (Woods and Teuber 1978). A quantitative measurement is probably necessary in order to establish a relationship (if any) between clinical assessments and severity of MM, since the amount of mirror activity could vary depending on the strength of the intentional motor activity of the opposite hand. Overall, it is important to investigate whether MM can be quantified and have any impact on hand function in children with early brain lesions. Due to simultaneous hand movement during MM, children with severe MM are likely to encounter difficulties in performing bimanual tasks where two hands are supposed to exert different force coordination, e.g., using a knife and fork, typing, and keyboarding. The extent to which the (symmetrical) mirror movements affect the performance of asymmetrical bimanual movements is largely unknown.

1.2 CORTICAL CONTROL OF HAND MOVEMENT

1.2.1 Organization of motor system

The human brain has four cortical primary and secondary motor areas, which contribute to the control of hand movement (Roland and Zilles 1996), (1) the primary motor cortex, M1, which is also termed as Brodmann’s area 4 (BA 4), (2) the supplementary motor area (SMA), (3) the lateral premotor cortex (PM), and (4) the cingulated motor area (CMA). About 40 percent of the corticospinal projections originate from the primary motor cortex, about 30 percent originate from the secondary motor areas and the rest come from postcentral sensory areas (Geyer et al. 2000). Thus, apart from morphological abnormalities of corticospinal tract, impairments in functional connectivity within the affected cortical areas could be an important determinant for motor function (Lee et al. 2011). The integrity of the corticospinal tract is crucial for voluntary hand movement and object manipulation (Lemon and Griffiths 2005). Typically, about 90 percent of the fibers cross the midline at the pyramidal decussation of the medulla and continues as lateral corticospinal
tracts, but about 10 percent of the uncrossed fibers continue ipsilaterally as the anterior corticospinal tracts. However, in newborn infants there are bilateral innervations (both contralateral and ipsilateral) from each motor cortex and the ipsilateral projections are expected to be gradually withdrawn as part of normal development (Eyre et al. 2001; Martin 2005; Eyre et al. 2007a). This withdrawal of ipsilateral projection has been discussed as “activity dependent competition for spinal synaptic space between the two hemispheres” (Eyre 2003). However, the presence of fast conducting ipsilateral corticomotor-projection from the unaffected hemisphere to the paretic hand as determined by transcranial magnetic stimulation (TMS) is frequently evident after perinatal brain injury (Figure 1), such as in cerebral palsy, and discussing that phenomenon in relation to hand function is one of the major aims of this thesis.

There is a somatotopic organization of body parts in both the pre and the postcentral gyrus. When motor fibers descend through the corona-radiata and pass through the anterior and posterior limbs of internal capsule, that somatotopy is still maintained. Fibers from the hand area lie at the posterior limb of internal capsule (PLIC), and the importance of this anatomical location in relation to the ventricular wall has been discussed, comparing impairments of upper limb and lower limb function (Staudt et al. 2000). All cortical motor areas send projections to the basal ganglia and the cerebellum, creating a loop of connections to and from the cortex via the thalamus and involve gray-matter structures. The thalamus is known to be the sensory relay center, receiving the major input through spino-thalamic tracts that carry primary sensory afferents (5%-10%), while the remaining 90-95% of synapses are from other locations, including the cortex, brain stem, local inter-neurons and thalamic reticular nucleus (Basso et al. 2005). Basal ganglia play a crucial role in the planning and execution of intended movements (Juenger et al. 2008). Lesions of the basal ganglia and/or the thalamus are frequent in children with cerebral palsy (Feys et al. 2010) and can have large negative impact on both development of hand function and on outcome of intensive training.

1.2.2 Neural control of bimanual coordination

Although in unilateral CP brain lesions are predominant in one hemisphere, the ability of the two hands to work together does not completely rely on the functional ability of each hemisphere alone. It is crucial that the information from one hand is transferred to the brain, in order to adjust activity in the other hand. CP is a result of a wide spectrum of CNS abnormalities, and lesions might cause disruptions in the neural network that controls bimanual activities.
In a review describing the neural interactions of bimanual coordination, Swinnen et al. argued that “the control of bimanual coordination cannot be assigned to a single locus; rather, it seems to involve a distributed network in which interactive processes take place between many neural assemblies to ensure efferent organization and sensory integration” (Swinnen 2002).

Moreover, a complex bimanual task would require precise temporal uncoupling, visuospatial coordination, appropriate generation and scaling of grip force for a successful task completion. These are known to be mediated via a fronto-parietal cortical motor network (Swinnen and Wenderoth 2004). Several neuroimaging studies have described the cortical regions that are involved in bimanual coordination by looking at the activation patterns during different modes of coordination (Stephan et al. 1999; Ullen et al. 2003; Aramaki et al. 2006) or by making a comparison between bi- and single-limb coordination (bimanual vs. unimanual) (Koenke et al. 2004). Besides primary motor (M1) and sensory cortex (S1), the specific role of the premotor cortex (PMC) (Koenke et al. 2004; Dafotakis et al. 2008), supplementary premotor areas (SMA) (Wiesendanger and Serrien 2004), cingulated motor areas (CMA), cerebellum and basal ganglia are well established for asymmetrical bimanual finger movement (Ullen et al. 2003; Prodoehl et al. 2009).

1.2.3 Grasping and lifting

In typically developing children, synergy between grip and load force is achieved at the age of approximately 6-8 years that enables smooth finger movement (Forssberg et al. 1991), and the ability to use information in an anticipatory way when grasping is achieved at the age of 8-11 years (Forssberg et al. 1992). In order to perform a grip lift task, first a stable grip should be established, followed by grip and load force increase (Gordon et al. 1993). Moreover, sensorimotor control ensures adequate adaptation of force output even when the weight or friction of the object is unknown (Johansson and Westling 1984; Forssberg et al. 1991; Forssberg et al. 1995). Children with cerebral palsy frequently do not develop coupling between the grip and load forces (Eliasson et al. 1991; Eliasson et al. 1992). Grasping objects using a precision grip is associated with neural activation within a large bilateral network of fronto-parietal areas, including the contralateral primary motor cortex (M1), the ventral premotor cortex (PMv) and the anterior intraparietal area (AIP) of the intraparietal sulcus (Ehrsson et al. 2000; Kuhtz-Buschbeck et al. 2001). Forssberg et al. (1999) suggested that in children with CP there is no strict cortical representation of grip-lift synergy and after an early lesion. The
neurons in one cortical area can be compensated for by neurons in other parts of the system to maintain function synergy (Forssberg et al. 1999).

1.3 CNS LESIONS IN RELATION TO PATHOLOGY AND MOTOR FUNCTION

In this thesis we have used conventional structural MRI to describe the type, location and extent of brain lesion, and the possible relationship with different aspects of hand function. MRI plays a significant role in characterizing the lesions in developing brain and in the diagnosis of CP (Bax et al. 2006; Towsley et al. 2010). A systemic review of studies of conventional structural MRI in children with CP could infer pathogenesis in only 85% cases. This however means that in about 15% cases MRI findings could be either normal or unspecific (Krageloh-Mann and Horber 2007).

Brain malformations underlying CP can be divided into two major subgroups: (a) malformations and (b) defective lesions (i.e. lesions characterized by tissue loss and gliosis). The defective lesions could be affecting the periventricular white matter and/or the cortical and subcortical gray-matter structures (Krageloh-Mann 2004; Krageloh-Mann and Cans 2009). Lesion types as seen in unilateral CP are white-matter damage of immaturity (WMDI), including periventricular leukomalacia (PVL) (34-36%), cortical or deep gray-matter lesions, mainly infarcts of the middle cerebral artery (31%) and brain malformation (10-16%) (Bax et al. 2006). The underlying lesions are often related to different periods of the brain development. The period involving the greatest risk of periventricular white-matter injury is 23-32 gestational weeks (Krageloh-Mann and Cans 2009). Interestingly, more than half of all children with CP are actually born at full term. Moreover, injuries that might have occurred earlier or later in pregnancy can have different entities. Lesions during the first and second trimesters often cause maldevelopment, whereas if they occur during the late second or early third trimester they can give rise to periventricular white-matter injury. Cortical and subcortical structures are more susceptible to injury around the time of birth (Accardo et al. 2004; Krageloh-Mann and Horber 2007).

Lesion characteristics of the CNS as seen in conventional structural MRI have been correlated to the development of hand function (Holmefur et al. 2012) and overall motor function (Wiklund and Uvebrant 1991; Staudt et al. 2000). Feys et al. have recently demonstrated that children with periventricular white-matter lesions have better hand function as measured using the Melbourne assessment, compared to those with gray-matter lesions (Feys et al. 2010). They also found that children with middle cerebral artery (MCA)
infarcts and lesions in the basal ganglia and thalamus had the lowest performance. In another cross-sectional study of 13 children with unilateral brain lesions (age 4-10 years), Forssberg et al. (1999) showed that the majority of them had not developed the force-coordination pattern typical for their age. The authors also found a correlation between the grip-lift synergy to the total extent of lesions in the contralateral hemisphere, white matter and lesions in the thalamus/basal ganglia (Forssberg et al. 1999).

Holmström and colleagues investigated 15 children with unilateral CP using diffusion tensor imaging (DTI) and found a strong correlation between fractional anisotropy (FA) measured in the corticofugal fibers and the performance of gross motor dexterity (Holmström et al. 2011). Asymmetry in corticospinal tract size, as measured by DTI (Bleyenheuft et al. 2007), or cross-sectional areas of the cerebral peduncles at the level of the mesencephalon have been shown to correlate strongly with manual dexterity, grip strength and stereognosis in children with unilateral CP (Duque et al. 2003).

1.4 SPASTICITY

Spasticity is a clinical condition, generally visible as tightness or stiffness in muscles, which commonly occurs as a consequence of lesions in the central nervous system. It is considered to be a major movement disorder seen in a large spectrum of neurological disorders, e.g., stroke (Bhimani et al. 2011), multiple sclerosis (Rekand and Gronning 2011) and spinal cord injury (Elbasiouny et al. 2010) and in children with cerebral palsy (Deon and Gaebler-Spira 2010; Chung et al. 2011). About one fifth or more of all stroke patients suffer from spasticity (Watkins et al. 2002; Pizzi et al. 2005). Unlike some of the early “negative” features of upper motor neuron lesions, i.e., weakness, loss of dexterity and fatigue, spasticity is considered to be a “positive feature” that develops at least some weeks after an acute stroke (Pizzi et al. 2005; Sheean and McGuire 2009).

A “proper” definition of spasticity has been debated over the years among clinicians and researchers (Pandyan et al. 2005; Malhotra et al. 2009; Elbasiouny et al. 2010). The most commonly used definition of spasticity was provided in 1980 by Lance (Lance 1980):

“Spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome.”
1.4.1 Pathophysiology of spasticity

The main contribution to a velocity-dependent increase of resistance to muscle stretch is given by the hyperexcitable stretch reflex (Ivanhoe and Reistetter 2004; Pandyan et al. 2005; Nielsen et al. 2007). Stretch reflex is a physiological property of our basic homeostasis system that helps muscles to maintain a steady state. For example, while lifting a weight, it would require a contraction of the flexor muscles (agonist) to pull the load through a simple motor command. This will stimulate muscle spindles to convey sensory monosynaptic input to the alpha-motor neuron in the spinal cord and modulate muscle activity. The antagonist group of muscles are inhibited via inhibitory interneurons to prevent any co-contraction and to perform the task smoothly (Bhimani et al. 2011). Both these actions occur though the same reflex arc, which is over-activated after a cortical lesion and a lesion to the descending motor pathways. An imbalance between the supra-spinal excitatory and inhibitory signals to the spinal circuitry has been discussed as influencing the increase in gain of spinal reflex pathways that leads to hyperactivity of spinal reflex and causes increased resistance to passive movements (Sheean and McGuire 2009). Hypertonia is also associated with muscle contracture (Odwyer et al. 1996) and microscopic structural changes (expanded connective tissue) (Olsson et al. 2006) in spastic muscles. There are the non-neural components of resistance, which are contributed by inertia, elasticity and viscosity (Lieber et al. 2003). The physical properties of the spastic muscle are changed over time and eventually develop muscle contractures that contribute to the increased resistance to passive muscle stretch (Pandyan et al. 2003).

1.4.2 Clinical assessment of spasticity

Spasticity is a one of the major symptoms following neurological injuries that clinicians commonly encounter in hospital settings. In addition to increased muscle tone, complications such as contracture of muscles, pain and weakness are frequently present together with functional limitation in everyday activities (Malhotra et al. 2008; Bhimani et al. 2011). The frequency and severity of these symptoms increase the burden on caregivers and therapists, and increase the challenge of evaluating and measuring spasticity for clinical decisions.

In a standard clinical setting, examiners quantify spasticity subjectively using the Ashworth scale (Ashworth 1964), by passively moving the affected limb and scoring according to the resistance felt by the examiners. The scale has subsequently been modified and presented as the modified Ashworth scale (mAS) (Bohannon and Smith 1987). The methodological limitations of the
Ashworth scale are frequently discussed (Platz et al. 2005; Hobart et al. 2007; Alibiglou et al. 2008; Fleuren et al. 2009), yet this is the most used method for measuring spasticity. Clinical rating scales only give an estimation of the total force. As mentioned above, besides the force resistance as a result of disinhibited tonic stretch reflex, there are also non-neural contributions to the resistance provided by inertia, elasticity and viscosity of the body part that is moved (Odwyer et al. 1996; Lieber et al. 2003; Olsson et al. 2006). If a proper quantification of the components of spasticity is to be achieved, the appropriate measurement would be to quantify both the neural and the non-neural components of spasticity (Kamper et al. 2003). In our study we have aimed to address that issue and validate a model for quantitative assessment of spasticity.

1.5 REORGANIZATION IN THE CENTRAL NERVOUS SYSTEM

1.5.1 Neuronal plasticity

Neuronal plasticity allows the central nervous system to reorganize neuronal networks in response to environmental stimulation, and to recover from brain and spinal cord injuries (Johnston 2009). The term plasticity is used to describe how the structure and function of neural circuits are modified in different instances, such as (a) during development, (b) by experience and learning, and (c) in response to brain lesion (Forssberg 2008). The molecular mechanism behind neural plasticity has been linked to activity-dependent modification of synaptic connectivity, including an increased number of synapses, long-term potentiation (LTP) and long-term depression (LTD) (Luscher et al. 2000; Trachtenberg et al. 2002; Malenka 2003).

The representation of the body parts in the sensory or motor cortex is known to be remodeled in a use-dependent manner. Animal studies have also shown such a reorganization of sensory and motor maps. In their seminal study, Hubel and Wiesel (1970) showed evidence of neural plasticity in the visual cortex of kittens, when they were visually deprived in one eye by suturing the eye lids for various periods of time (Hubel and Wiesel 1970). In rats, limb immobilization that reduces tactile input leads to a reduced somatosensory area (Coq and Xerri 1999). Nudo et al. studied the training effect of a specific motor task on the cortical maps of the upper limb in monkeys, using TMS and muscle electromyography (Nudo and Milliken 1996; Nudo 1999). Monkeys were given different tasks, which would require them to use different groups of muscles in the upper limb. They found that only the cortical area representing the training muscles was enlarged, whereas the area
representing a proximal muscle was reduced. Expansion of the whole cortical map was only achieved when the task was performed repeatedly, and assumed that the synaptic connectivity of the cortical circuit was strengthened.

After temporary differentiation in the fingers, an increased somatosensory evoked field (SEF) was shown in the neighboring non-deafferented body parts (Rossini et al. 1994a). Amputation of the body part also resulted in increased corticomotor excitability of body parts proximal to the area representing the amputated part (Cohen et al. 1991). Influence of age in activity-dependent plastic changes in the motor cortex has been shown in other studies, where a correlation was found between the cortical sensory-motor representation and the age at which skilled piano players begin to play (Pantev et al. 2001; Bengtsson et al. 2005).

The examples above highlight the fact that the central nervous system has enormous abilities to change in an attempt to compensate for and preserve functional abilities.

1.5.2 Reorganization in children with unilateral CP

The developing nervous system has a greater ability to go through sensorimotor reorganization to various extents, which is likely to be a compensatory mechanism in order to develop and preserve functional abilities after brain lesions that occurred at an early stage of life (Maegaki et al. 1997; Thickbroom et al. 2001; Staudt et al. 2002; Vandermeeren et al. 2009; Wilke et al. 2009; Staudt 2010a). Such a phenomenon was first described in the motor cortex of monkeys by Kennard in 1936, known as Kennard’s principle (Kennard 1936). Later, from a cross-sectional study on 33 children with unilateral cerebral palsy, Carr at al., also reported reorganization of the central motor pathway (Carr et al. 1993) and similar results were also shown from a longitudinal study where children were studied from birth and following them up longitudinally for two years (Eyre, 2001). Over time, increased research interest and methodological advancements in neurophysiology (TMS, navigated TMS, SEP, MEG) and neuroimaging (MRI, fMRI, DTI, PET) have improved our understanding of sensorimotor reorganization significantly. It is important that we have a clear insight into the mechanism of underlying functional recovery, if we want to develop a rational rehabilitation method for motor recovery in children with CP (Ragazzoni et al. 2002).
The typical corticomotor-projection is contralateral, meaning that the muscles of each side of body are innervated by descending fibers from the contralateral hemisphere (Figure 1A). With the use of transcranial magnetic stimulation (TMS) it has been shown that, besides typical contralateral motor projection patterns, there can also be two other types of organization, whereby the paretic hand receives corticomotor-projection from (a) mixed, i.e., from both contralateral and ipsilateral hemispheres (Figure 1B), or (b) ipsilateral, i.e., only from the unaffected hemisphere (Figure 1C) (Carr et al. 1993; Carr 1996; Maegaki et al. 1997; Thickbroom et al. 2001; Staudt et al. 2002; Vandermeeren et al. 2009). Possible mechanisms for the development of ipsilateral projection have been indicated, which are, (1) fibers originating from the abnormal branching of contralateral axons, e.g., through corpus callosum or (2) preservation of fetal connections that persisted without normal regression (Maegaki et al. 1999; Staudt et al. 2002). In addition to the neurophysiological approaches, neuroimaging studies using functional MRI (Vandermeeren et al. 2002a; Staudt et al. 2004a) and positron emission tomography (PET) (Vandermeeren et al. 2002b) have also yielded similar evidence of functional reorganization in children with unilateral brain lesions. In an fMRI study, Vandermeeren and colleagues investigated brain activation with a unilateral sequential finger-to-thumb opposition task in six children with unilateral upper limb impairment, and showed that movement of paretic fingers activated both hemispheres, with a strong ipsilateral predominance of the unaffected hemisphere, as compared to healthy controls (Vandermeeren et al. 2003a).

The level of maturation of the brain at the time of injury has been discussed as having an influence on the level of reorganization (Staudt et al. 2004b; Cioni et al. 2011). During the perinatal period, the neuronal tissues remain vulnerable to any type of injury. Myelination takes place at this time and neuronal death from apoptosis is more frequent than at any other period, for which the possibility of any plastic change in the central nervous system is also higher (Cioni et al. 2011). In an earlier study, Staudt et al. reported that the efficacy of sensorimotor reorganization with ipsilateral corticomotor-projection decreased significantly in children who acquired lesions during the late third trimester of pregnancy. The earlier the prenatal and perinatal brain lesion is acquired, the better the prognosis regarding hand motor abilities in general (Staudt et al. 2004b).
Figure 1: Schematic diagram showing patterns of corticomotor-projections as determined by transcranial magnetic stimulation (TMS). “P” denotes paretic hand, which can receive contralateral projection from affected hemisphere (A), mixed projection from both affected and unaffected hemisphere (B), ipsilateral projection from unaffected hemisphere (C).

Physiologically remnant ipsilateral motor projection has explained the presence of mild/moderate mirror movements in typically developing children (Mayston et al. 1999; Cincotta and Ziemann 2008). In a pathological situation, the presence of prenatal/perinatal injury may possibly drive the preservation of the ipsilateral projection, as a physiological effort of the developing nervous system to preserve motor function. It is also true at the same time that the ipsilateral corticomotor-projection might be withdrawn with age (Eyre et al. 2001), leaving the window open for discussion about the functional utility of having a reorganized corticomotor-projection in the first hand. In several studies, a negative correlation between the motor function and ipsilateral projection has also been indicated (Thickbroom et al. 2001; Staudt et al. 2002).

Even though the descending motor tracts can be reorganized, the sensory tracts are known to preserve their typical contralateral orientation. However, only a few studies have claimed the possible reorganization of ascending sensory tract in a small number of participants, where results showed ipsilateral sensory projection from paretic hand to unaffected hemisphere (Maegaki et al. 1995; Nevalainen et al. 2012). Conversely, several studies using
SEP (Guzzetta et al. 2007), MEG and fMRI (Staudt et al. 2006) consistently found sensory organization to be preserved from paretic hand to contralateral affected hemisphere. So, it is important to consider the functional relevance of inter-hemispheric dissociation when there is ipsilaterally reorganized motor and contralaterally preserved somatosensory function. Such dissociation might have a negative effect on hand function, since sensorimotor integration is important for the execution of any motor task.

The section above aimed to describe the pathology and physiology behind sensorimotor reorganization. Whatever the pathology behind sensorimotor reorganization or mechanism within such organization, the focus of my thesis is of course to investigate whether such a consequence would have any role on hand function (unimanual, bimanual) and outcome after intensive treatment, e.g., CIMT.

The presence of a relatively inert affected hemisphere, alteration of corticomotor-projection patterns, the possibilities of an imbalance of inter-hemispheric inhibition and inter-hemispheric dissociation have made sensorimotor organization a crucial and interesting topic to investigate for both neurophysiologists and clinicians.

1.6 CONSTRAINT-INDUCED MOVEMENT THERAPY (CIMT)

Constraint-induced movement therapy (CIMT) is an intervention method that aims to improve functional abilities of paretic upper limbs in individuals with unilateral impairment. Since its introduction, CIMT has been found to be a very promising therapy in both adults with stroke (Taub et al. 1994; Wolf et al. 2006; Sirtori et al. 2009) and children with cerebral palsy (Eliasson et al. 2003; Bonnier et al. 2006; Hoare et al. 2007; Eliasson et al. 2009). A positive outcome in the upper limb function after CIMT has also been indicated in children with unilateral impairment from other etiologies, such as after traumatic brain injury (Cimolin et al. 2011), obstetric brachial plexus injury (Buesch et al. 2010) and hemispherectomy (de Bode et al. 2009). The key elements of CIMT are: (1) constraining the use of the less-impaired upper limb, by using casts, resting splints, slings, etc., (2) encouraging the use of the affected hand, and (3) intensive, repetitive, daily, and therapist-directed practice of motor activities with the impaired upper limb for an extended period. However, modifications have been made to the original protocol to make the intervention more children- friendly, e.g., modified CIMT (m-CIMT) for younger children where training is offered for fewer hours per day over a longer period (Eliasson et al. 2005). Very recently, eco-CIMT has been proposed, whereby training can be
implemented by the child’s parents and/or preschool teacher, instead of the child’s regular therapist (Eliasson et al. 2011).

1.6.1 The background to CIMT

Immediately after the acute phase of any neurological insult, the performance of the affected limb is decreased and further attempts to use that limb are therefore avoided or suppressed. This behavioral phenomenon is defined as “learned non-use”, and was described from an animal study by Dr. Edward Taub (Taub 1976). In that study, abolishment of sensory inputs after dorsal rhizotomy in monkeys made them stop using the affected arm. It was observed that the movements of the deafferented monkeys were clumsy and often lacked precision in timing compared to those of the normal. However, with specific training, the deafferented monkeys could perform almost any sequence of movements of which a normal animal is capable (Taub 1976; Taub et al. 1980). Subsequently, this principle was used to develop and introduce constraint-induced movement therapy (CIMT) as an intervention method (Taub et al. 1994; Taub et al. 2004).

1.6.2 CNS plasticity and CIMT in children

It would seem that CIMT is an ideal way to provide intensive practice in unilateral CP, but there are a number of key considerations in the application of CIMT to children. Research interest in CIMT has grown over the years, looking at the efficacy of the therapy in children (Gordon et al. 2006b; Huang et al. 2009) and factors that might influence the outcome (Charles and Gordon 2005; Barzel et al. 2009; Brady and Garcia 2009). Although there are many small sample studies, CIMT has still not been studied to the same extent in children as in adult with stroke (Gordon 2011).

Typically, rehabilitation techniques focus on reinforcing compensatory strategies to encourage the use of the paretic upper extremity, whereas CIMT primarily targets the unaffected upper limb. Despite the similar behavioral mechanisms as identified in adults, Eliasson at al. suggested that the learned non-use may be a different phenomenon in children who sustain an early brain lesion (Eliasson et al. 2003). From a neurophysiological point of view, CIMT in children should not be considered to be exactly the same as in adults. Children, in contrast to adults, may have never learned to use their upper limb effectively to start with. So, the point of developmental disregard and/or learned non-use of their impaired limb might be a different issue in children with early brain lesions (Gordon et al. 2005). Together with the potential of
reorganized corticomotor-projection and physiology behind CIMT, it is plausible that the outcome of CIMT in children with unilateral CP might be influenced by the plasticity of the central nervous system. A possible relationship between hand function and brain lesion is described in detail in the sections above. The effects of brain lesion characteristics on the outcome of intensive training in children with unilateral CP are not well investigated.

The combined use of transcranial magnetic stimulation (TMS) and neuroimaging has improved our understanding about cortical plasticity in relation to CIMT. In 1998, Liepert and colleagues were the first to report neurophysiological changes in the brain as assessed with TMS in response to CIMT in adult stroke patients (Liepert et al. 1998). They not only found an increase in the number of scalp locations that produced MEP in the paretic hand, but also showed the ipsilesional motor map to be enlarged after CIMT. Later, in another study it was shown that the degree of map expansion correlates with improvement in some measure of motor activity after CIMT (Sawaki et al. 2008). Similar information on children with CP is not yet reported. However, there are methodological limitations in carrying out extensive TMS investigation in a pediatric population.

In regard to reorganized corticomotor-projection (as described with TMS), Kuhunke et al. (2008) raised a valid question, whether children with ipsilateral corticomotor-projection would improve different than with other projection patterns. They argued that children with ipsilateral motor projection pattern would have a) interhemispheric dissociation, i.e., reorganized corticomotor-projection but preserved contralateral somatosensory tract, and b) an imbalance in transcallosal inhibition due to unilateral brain lesion (Kuhnke et al. 2008). We have addressed a similar question in Study II, which will be discussed in a later section.

**Efficacy of CIMT**

Improvement of hand function after CIMT and modified CIMT in children with unilateral CP has been reported in several studies. A Cochrane review has also indicated a somewhat positive effect, although the review was based on very few randomized controlled trials (Hoare et al. 2007). Even though the focus of the thesis does not directly permit the discussion of all factors that might influence the efficacy of CIMT, it is still of scientific and clinical interest to raise this question.
There are growing numbers of publications showing a wide range of outcomes after CIMT in children. However, it is of great important to investigate why, with the same treatment, some children improve their hand function, whereas others do not. Such individual variations in results still lack reasonable explanations. Many factors, such as the duration and intensity of training, types of restraint, the length of the restraint time, the practice regimen used during the intervention, the training environment (e.g. at home or in a clinical setting) and the age at the time of training, have been discussed frequently in terms of their influence on training outcomes (Charles and Gordon 2005; Boyd et al. 2010; Eliasson et al. 2011; Gordon 2011). Gordon and colleagues found no difference in training effect between children at 4–8 years of age and 9–13 years of age (Gordon et al. 2006b). Eliasson and colleagues have demonstrated a good effect from 18 months to four years of age and in teenagers (Eliasson et al. 2005; Bonnier et al. 2006; Eliasson et al. 2009). Studies published so far lack adequate information on individual characteristics that are related to a positive outcome of CIMT. Hoare and colleagues emphasized individual variations in factors such as the participant’s baseline characteristics, behavior, side of hemiplegia and site of lesion, all having a potential impact on CIMT outcome (Hoare et al. 2007). Moreover, the possibilities of sensorimotor reorganization in children with early brain lesions make these questions even more relevant. Restraining the child’s non-paretic extremity as a part of early intensive treatment possibly even risk a damage to the restrained better functioning arm (Gordon 2011).

In a very recently published study, Xu and colleagues (Xu et al. 2012) used concurrent electric stimulation together with CIMT and showed further improvement of hand function. Such information opens up the possibility of other neuromodulation techniques, such as repetitive TMS, as an adjuvant to facilitate the efficacy and outcome of CIMT.
2 AIMS OF THE THESIS

The overall aim of this thesis is to investigate the relationship between hand function and different types of unilateral brain lesions from the perspective of development, training outcomes and clinical measurements.

The specific aims of the studies are -

- To investigate the relationship between hand function, brain lesions and corticomotor-projections in children with unilateral cerebral palsy, Study I.

- To explore if hand function can be improved regardless of corticomotor-projection pattern and brain lesion characteristics in children who are typically included in constraint-induced movement therapy (CIMT), Study II.

- To investigate coordination of fingertip forces during an asymmetrical bimanual task in children with unilateral cerebral palsy, Study III.

- To develop and validate a new method to measure spasticity that can be easily used in clinical practice, Study IV.
3 MATERIALS AND METHODS

3.1 STUDY OUTLINES

Study I

This is a cross-sectional study. A convenient sample of 17 children with unilateral CP was assessed for unimanual and bimanual hand function. All participating children were in gross motor function classification system (GMFCS) level I (Palisano et al. 1997). Neuroimaging (MRI) and neurophysiological (TMS) data were later collected at the core medical facility of Karolinska University Hospital, Stockholm.

Study II

Twenty-six children with unilateral CP, who participated in CIMT day camps, were screened for eligibility for TMS and MRI investigations. See also (Eliasson et al. 2009). Sixteen participants were included in this study (Table 1). One participant was in MACS level I and the rest were in MACS level II (Eliasson et al. 2006).

The duration of a camp was two weeks, and children underwent intensive training for seven hours per day during the weekdays (a total of ten days). The content of the program was based on different recreational activities and the participants wore a restraining glove on their non‐paretic hand (Eliasson et al. 2009). Activities were supervised by occupational therapists, physical therapists and volunteers. Clinical assessments (Table 2) were carried out before and after the camps by an occupational therapist, who was not actively involved in the day camps.

Study III

In an experimental study, fingertip forces during an asymmetrical bimanual task in children with unilateral cerebral palsy (n=12) were compared to those of typically developed participants (n=15) (Table 1). Both force and temporal coordination patterns were compared (Figure 3). Furthermore, mirror movements (MM) were assessed quantitatively (Kuhtz-Buschbeck et al. 2000) to check the extent to which the (symmetrical) mirror movements affect the performance of asymmetrical bimanual movements. Dexterity, sensibility, and spasticity were also assessed.
Study IV

This study was designed to validate a biomechanical model that quantifies different components of spasticity (Table 4). The sample included 31 adults with chronic stroke and 11 healthy volunteers for control data (Table 1). An ischemic nerve block paradigm was used on a subgroup of stroke patients (n=7). The study was conducted at the department of clinical neurophysiology, Karolinska Hospital, Solna.

3.2 SUMMARY OF THE PARTICIPANTS AND THE RECRUITMENT PROCESS

In all four studies we have investigated participants with hemiplegia due to unilateral brain lesions in both children and adults. We have included children with unilateral CP (Studies I, II and III) and adults with chronic stroke (>6 months) (Study IV), depending on the research question and methods used for the respective study. An overall summary of characteristics of participants is presented in Table 1.

Table 1: Summary of study aims, number of participants and variations in age in different studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Number of participants</th>
<th>Age of the participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>To study correlation between hand function, brain lesion and corticomotor-projections</td>
<td>Unilateral CP, n=17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mean age 11.4y, [SD 2.4y], range 7–16y</td>
</tr>
<tr>
<td>II</td>
<td>To study the effect of corticomotor organization and brain lesion characteristics on the outcome of CIMT</td>
<td>Unilateral CP, n=16&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Mean age 13y [SD 2.0y], range 10–16y</td>
</tr>
<tr>
<td>III</td>
<td>To study finger tip force coordination during an asymmetric bimanual task</td>
<td>Unilateral CP, n =12&lt;sup&gt;b&lt;/sup&gt; TDP, n = 15</td>
<td>Mean age 14.4y, [SD 3.3y], range 9–20y</td>
</tr>
<tr>
<td>IV</td>
<td>To develop and validate a new method to measure spasticity to use in clinical practice</td>
<td>Chronic stroke, n= 31 Healthy volunteers, n=13</td>
<td>Mean age 61.3y [SD 10y], range 39.5–77.8y</td>
</tr>
</tbody>
</table>

<sup>a</sup> Four participants from Study I were also included in Study II
<sup>b</sup> One participant from Study II was also included in Study III
All participants, irrespective of the studies, were recruited from Stockholm county council.

For Studies I, II and III, a similar recruitment procedure was followed. First a written invitation to participate in the study was distributed to potential participants through their therapists. Once families showed an interest in taking part in the study, a letter with detailed information about the study was sent to them. Families were contacted again by telephone to check for exclusion/inclusion criteria and also to answer their questions regarding the study. For Study IV, patients with chronic right-sided spastic hemiparesis following stroke were recruited from the rehabilitation clinic and from an outpatient clinic specialized in neurological rehabilitation in the greater Stockholm area. The method of recruitment was similar to the above, i.e., a) identification via medical staff and medical records, b) sending out information letter and c) telephone call.

3.2.1 Inclusion/exclusion criteria

Participants with a wide range of hand functions were included in Study I. Individuals with metallic parts in the body were excluded primarily for both MRI and TMS sessions. Moreover, specific exclusion criteria, i.e., (1) uncontrolled epilepsy and (2) metallic dental braces, were applied for TMS experiments, in accordance with the guideline from the TMS safety consensus meeting, Siena (Italy) on March 7–9, 2008 (Rossi et al. 2009).

All participants included in Study II were expected to have a minimum motor function of being able to grasp and lift a 500 gram bottle with their paretic hand. This ensured a minimal level of grasping ability and strength, which made them suitable candidates for CIMT. Exclusion criteria for TMS experiments and MRI investigations were as described above for Study I.

The tasks in Study III required the participants to grip and lift two devices in the air. Having sufficient grasping ability and strength to lift and hold one large device (325 gm) with one hand and place a smaller device (150 gm) on the top with the other hand was thus considered a major inclusion criterion.

In Study IV, chronic stroke patients (>6 months) with right hemiparesis were included. Selectivity of the paretic side was primarily due to the fact that the custom-built device used in the study allowed measurements only from the right upper limb. Specific exclusion criteria were (a) previous neurological disorder, (b) inability to communicate and understand the information
included in the study, (c) less than 40° passive extension of the right wrist (to avoid fast stretches near the end of the movement range), and (d) present pharmacological treatment of spasticity.

3.3 CLINICAL MEASUREMENTS OF UPPER LIMB FUNCTION

A wide range of hand function tests were used across the studies, investigating different extent of motor (unimanual and bimanual) and sensory abilities, which are summarized in Table 2 and described in later sections.

Table 2: Summary of the clinical measurements of sensory and motor functions of the upper limb

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assisting hand assessment</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Box and Blocks</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2PD</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Mirror movements</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JTHFT</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melbourne assessment</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAS</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>UL-MAS</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Grip strength</td>
<td></td>
<td></td>
<td>x</td>
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<tr>
<td>Fügl-Meyer Assessment</td>
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<td>x</td>
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</table>

3.3.1 Assisting hand assessment (AHA)

We used AHA to measure how effectively the participants use their paretic hand in bimanual activities (Krumlinde-Sundholm et al. 2007; Holmefur et al. 2009). This test is validated for children between 18 months and 12 years, so a research version was used for participants over 12 years of age. The AHA has 22 items rated on a 4-point scale, videotaped and scored in a 22-88 raw score range. The raw scores are converted to interval level data by means of a Rasch analysis, and linearly-rescaled Rasch measures with the range 0-100 AHA-units were obtained in which a higher number indicates a higher ability (Study II).

3.3.2 Box and Blocks (B-B)

The Box and Blocks test is a timed test that assesses gross unimanual dexterity for each hand separately. Participants are asked to move as many blocks as possible in 60 seconds from one side of a box to the other, passing over a 12 cm high partition (Mathiowetz et al. 1985).
3.3.3  **Assessment of two point discrimination (2PD)**

This is a test to measure tactile discrimination at two points on the fingertips (Moberg 1990). Tactile discrimination of at least 3 mm is considered normal, decreased when 5 mm of spacing is discriminated and poor when the participant is not able to discriminate at 5 to 7 mm spacing. This test was used in Studies I and III.

3.3.4  **Assessment of mirror movements (MM)**

Mirror movements were assessed with three repetitive tasks: opening and closing of the fist, opposition of index finger and thumb, and sequential finger opposition. These tasks are performed with one hand while the other hand remains inactive. The sessions were videotaped and later analyzed to detect possible mirror movements in the non active hand, which was categorized using the scale of Woods and Teuber (1978): 0=no clear imitative movements; 1=barely discernible repetitive movements; 2=slight mirror movements or stronger, but briefer, repetitive movements; 3=strong and sustained repetitive movements; 4=movements equal to that expected for the intended hand (Woods and Teuber 1978).

3.3.5  **Jebsen-Taylor hand function test (JTHFT)**

In Study IV we used a modified version of JTHFT, which had six subsets in total (writing excluded) (Jebsen et al. 1969; Taylor et al. 1973). Participants were instructed to perform the tasks as rapidly and accurately as possible, and scores were recorded in seconds. The maximum time allowed to complete each task was reduced to two minutes, which is different from the original protocol of three minutes, in order to reduce the level of frustration associated with failure to accomplish the task (Gordon et al. 2006b). The sum score of six subsets is used as the result.

3.3.6  **Melbourne assessment of upper limb function**

This is a 16-item, assessment tool that measures quality of movements in upper limb motor function for children with neurological impairments. Test items included are representative of significant components of unilateral upper limb function, e.g., reach, grasp, release, manipulation, and also specific difficulties, e.g., ability to reach the bottom or mouth with the assessed hand (Johnson et al. 1994; Randall et al. 2001). The test is videotaped for further analysis and the raw score sum is converted to a percentage scale (1-100).
3.3.7 Modified Ashworth scale (mAS)

Spasticity is clinically measured using the modified Ashworth scale (Bohannon and Smith 1987). In this method, muscle spasticity experienced in three passive movements was assessed, i.e., elbow extension, wrist extension and supination. The ratings for the three joints was summated to give a total score range. In adults, assessment using the modified Ashworth scale ranges from 0 to 4 (Study IV). Another modified scoring that ranges from 0 to 5 was used for the pediatric population in Study III (Krumlinde-Sundholm and Eliasson 2002).

3.3.8 Upper limb motor assessment scale (UL-MAS)

The upper limb subsection of the motor assessment scale (UL-MAS) was used to measure gross and fine motor function of the upper extremity in Study IV. The score includes eight different items representing eight areas of motor function and one item related to muscle tone on the affected side. Each item is scored on a seven-point scale from 0 to 6 (Carr et al. 1985; Lannin 2004).

3.3.9 Grip strength

Grip strength was measured using a commercially available device Grippit® dynamometer (AB Detektor, Gothenburg, Sweden) (Hager-Ross and Rosblad 2002). Participants are instructed to grip the instrument handle as strongly as possible for ten seconds and the device measures isometric grip strength in newton (N).

3.3.10 Fügl-Meyer Assessment

This is a multi-item scale divided into five domains: motor function, sensory function, balance, joint range of motion, and joint pain. Each domain is scored on a three-point ordinal scale (0 = cannot perform, 1 = performs, partially, 2 = performs fully) (Fugl-Meyer et al. 1975; Gladstone et al. 2002). We used the sensory domain to check for the participant’s ability to discriminate between sharp and dull sensory stimulus.

3.4 NEUROPHYSIOLOGY

TMS is performed in the neurophysiology clinic as a routine investigation, yet we made minor modifications to the protocol to suit our research question and the study population. A brief description of the physiology behind TMS and data collection procedures is mentioned below.
3.4.1 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a painless and non-invasive method of stimulating cortical neurons (Barker and Jalinos 1985; Platz and Rothwell 2010; Ziemann 2011). In this method, a magnetic field generator sends a current that lasts about 1 ms, through an induction coil placed on the scalp (Figure 2). The current creates a magnetic field that is perpendicular to the coil, which passes through the skull and induces an eddy current within the brain, again parallel to the coil. The peak strength of the magnetic field is related to the magnitude of the current and the number of turns of wire in the coil. If a sufficient intensity of stimulation is used, and the coil is held over the motor cortex, the electric field can generate action potentials in the cortical neurons just beneath the coil. The descending volleys are produced in the corticospinal pathway, and the resulting activation of the target muscles which is termed as MEP (motor evoked potentials) can be recorded by placing surface electrodes on the muscle belly.

Figure 2: Schematic representation of a TMS circuit (Reproduced with permission of Dr. Richard E Frye) (Frye et al. 2008). The electric power supply charges the capacitor. An operator or computer then signals for the charge stored in the capacitor to be released into the stimulation coil through a switch. The current flowing through the stimulating coil (circular/figure of eight) produces a perpendicular magnetic field which transverses the skull and induces electrical currents within the cortex underlying the coil. A detectable muscle contraction, typically in a contralateral limb, results if the stimulation coil is placed over the motor cortex at the correct angle. This motor response is quantitatively measured as the motor evoked potential (MEP).
Eddy current induced excitation occurs at the site where axons terminate or bend sharply, if they are in the relatively uniform electric field of the TMS coil (Amassian et al. 1992; Maccabee et al. 1993). A stimulator can develop about 1.5 – 2.7 tesla (T) at the face of the coil in a brief period of time (1 ms) and appear to be able to activate cortical neurons at a depth of 1.5 – 2 cm beneath the center of the coil. Figure 2 shows schematically the components of a basic TMS paradigm.

In a single pulse TMS paradigm, magnetic stimulations are applied with an inter stimulus interval of approximately 6- 8 seconds with a focal figure of eight coil (Studies I and II) or circular coil (Figure 2). This paradigm is commonly used for mapping motor cortical outputs, studying central motor conduction time and causal chronometry in brain-behavior relations (Reis et al. 2008; Rossi et al. 2009; Groppa et al. 2012).

3.4.2 Data collection

Magpro X-100 stimulators, with a peak magnetic field strength of 2.5 T at 100% stimulator output with a figure of eight coil (model C-B60), 2 x 75 mm diameter (Medtronic Inc. Minneapolis; MN, USA) were used for both Study I and Study II. However, since our aim was to check for cortico-muscular responses from both hands at the same time, the experimental setup was modified and a different EMG system was used in Study II (Table 3).

Moreover, we adopted a protocol which gave reliable information about the type of projection pattern, while reducing the total number of necessary pulses (Holmström et al. 2010; Staudt 2010b). Primary motor area (M1) was initially identified on both cortical surfaces using an international 10-20 system and marked with a felt pen. Resting motor threshold was defined as the lowest stimulator output that could elicit a reproducible MEP (amplitude ≥ 50 µV) in the relaxed target muscle in five out of ten stimulations (Rossini et al. 1994b). The absence of MEP was confirmed when 100% stimulator output could not generate any MEP in a 2 cm radius around the optimal spot. The mean duration of the cortico-muscular latencies was measured and compared between sides. Stimulator parameters were the same, but different EMG systems were used between Studies I and II; Table 3 summarizes the main differences in the TMS experimental setup between the studies. TMS sessions were conducted at a core hospital facility, with access to safety measures for theoretically possible side effects.
Table 3: Methodological differences in TMS setup between studies

<table>
<thead>
<tr>
<th></th>
<th>EMG system</th>
<th>Target muscle</th>
<th>Surface electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>2 channel amplifier (Keypoint* system, Denmark)</td>
<td>Abductor Pollicis Brevis (APB) of both hands</td>
<td>Shallow cupped Ag/Ag Chloride surface electrodes (Nihon Kohden®, Roshbach, Germany)</td>
</tr>
<tr>
<td>Study II</td>
<td>4 channel amplifier Inomed IOM® device (Inomed GmbH, Germany)</td>
<td>Abductor Pollicis Brevis (APB) and first dorsal interosseous (FDI) of both hands</td>
<td>Ambu® Neuroline 715 silver/silver chloride sensor (Ambu A/S, Denmark)</td>
</tr>
</tbody>
</table>

3.4.3 Safety concerns for TMS

There is an international guideline for designing any type of TMS study. A consensus meeting organized at regular intervals (once approximately every ten years) (Wassermann 1998; Rossi et al. 2009), with the aim of 1) setting up a definite guideline for using TMS in both children and adults, 2) reviewing the issues concerning risk and safety of conventional TMS protocols, 3) addressing undesired effects, and 3) summarizing the reported adverse effects. The most recent meeting was held at Certosa di Pontignano, Siena (Italy) on March 7–9, 2008 (Rossi et al. 2009).

TMS pulse induces an action potential in the cortical neuron and, with repeated stimulation in a single session, there is a “theoretical” risk of inducing a seizure, but it is extremely rare or absent with paradigms such as in the single pulse stimulation used in our studies. Some minor adverse effects are often reported, e.g. headache, tinnitus, numbness of upper limbs, but those are regarded more as local side effects from sitting relatively still during the experiment than as direct effects of TMS. From our experience in Studies I and II, we have not encountered any local or remote side effects of using TMS in the pediatric population. Every time the stimulator generates a pulse, it also creates a high pitched clicking sound that has been reported to have some negative auditory effect in the participant (Counter et al. 1990). So, as recommended, we always used ear plugs during our experiments.

As far as children and younger adults are concerned (Gilbert et al. 2004; McClelland et al. 2011), TMS has been reportedly used in over 800 typically developed children and over 300 neurologically impaired children, and authors
have highlighted the absence of reported adverse effects in children, see the review by Frye and colleagues (Frye et al. 2008).

3.5 NEUROIMAGING

We have used conventional structural magnetic resonance imaging (MRI) to describe the characteristics of brain lesions for Studies I and II. All images were visually analyzed by the same neuroradiologist with a protocol that has been used in both Study I and Study II.

The MRI findings were grouped according to the primary pattern of damage, as follows: white matter damage of immaturity (WMDI), focal infarct and maldevelopment (Bax et al. 2006). The extent of periventricular white matter reduction was visually classified as mild, moderate or severe. The location of periventricular white matter and grey matter damage was reported. Basal ganglia and thalamus damage was defined as volume reduction. In children with bilateral lesions, only lesions of the most affected hemisphere were reported in detail.

3.6 MEASUREMENTS OF FINGERTIP FORCE

3.6.1 Grip devices

Two different sized, custom-made grip devices were used (Figure 3A). Both were equipped with strain-gauge transducers to measure the grip forces (GF) (Figure 3A). The two parallel contact surfaces (35 mm x 35 mm; 20 mm apart) of each device were covered with sandpaper. The small device (weight 150 g) had a handle and a wide base allowing it to be placed on the larger device (weight 325 g), which consisted of a platform (11 cm x 11 cm) on the top. The mean GF was calculated as (GF1+GF2)/2. The large device also measured the load force from the two contact surfaces (LF; tangential force) as (LF1+LF2).
3.6.2 Data collection and analysis

Before starting data collection, the task was demonstrated to the participants and they were also allowed to practice. The instructions were to grasp two devices in each hand between the thumb and the index finger, hold them in the air about 10 cm above the table surface for approximately five seconds and then slowly release the small device on the top of the larger device. Temporal and fingertip force parameters were recorded (Figure 3B). The same task was performed twice in two different series using alternate hands as either the releasing hand or the holding hand. Fifteen consecutive trials were performed for each series. The first five trials were practice trials and were excluded from the analysis. The experimenter replaced the devices between trials. In another task, the participants also held the devices in both hands. In another task, they were then asked to voluntarily compress a device in one hand, repeatedly with moderate force. But, grip force parameters were recorded from both hands, in search of possible mirror movements. Signals were sampled at 400 Hz to a computer terminal, and were evaluated interactively with custom-designed software (SC/ZOOM; Umeå University, Sweden).
3.7 ESTIMATION OF NEURAL AND NON-NEURAL CONTRIBUTIONS TO PASSIVE MOVEMENT RESISTANCE

3.7.1 Description of biomechanical model

The method is based on a model by Koo and Mak (2006) in which the resisting force produced during passive wrist extension can be regarded as a summation of passive elasticity, viscosity, and inertial forces, and by active muscle force, according to the following equation (Koo and Mak 2006).

\[ F_m(\theta) = F_p(\theta) + F_v(\theta) + F_r(\theta) + F_{in}(\theta) \]

Here, \( F_m \) is the total measured passive force, \( F_p \) is the passive elastic force, \( F_v \) is the viscous force, \( F_r \) is the reflex forces, \( F_{in} \) is the inertia forces of both the limb and the moving parts of the measuring device, and \( \theta \) denotes a specific angle that the joint is moved through. The time points along the force trajectory used for measurements are defined below and also illustrated in Figure 4.

- P1 = the first peak of the total force trajectory occurring earlier than 30 ms after movement onset (i.e. prior to the stretch reflex response).
- P2 = the force at the moment when the passive movement stops.
- P3 = the resisting force one second after completion of the slow velocity movement.

The force trajectory from a well controlled extension of the wrist and simultaneous recording of the resisting force is decomposed in multiple components that build up the total force, i.e., inertia (IC), viscosity (VC) and elasticity (EC), as well as a neural component of reflex mediated muscle contractions (NC) (Table 4). The model separates the active force of muscle contractions induced by the stretch reflexes from the passive mechanical components (Lance 1980; Powers et al. 1988; Ibrahim et al. 1993; Musampa et al. 2007). This is according to the definition of spasticity by Lance (Lance 1980), since the velocity-dependent muscle resistance is a fundamental factor in the increased muscle tone. Table 4 summarizes the model passive (inertia, viscosity) and active (neural) components of spasticity, and Figure 4 shows the variation of total force over time during the stretch in conjunction with the passive and active components.
Table 4: Summary of biomechanical model.

<table>
<thead>
<tr>
<th>Components</th>
<th>Measurements</th>
<th>Model</th>
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</thead>
<tbody>
<tr>
<td>Inertia component (IC)</td>
<td>Inertia is the force resisting the acceleration (a) of the hand, and depends on the mass (m) of the hand and movable platform and the acceleration.</td>
<td>IC = m × a</td>
</tr>
<tr>
<td>Viscosity component (VC)</td>
<td>The resisting force that remained after the inertia component (IC) had been subtracted from the initial peak of the total resisting force at P1</td>
<td>VC = (Total force_{P1} - IC) × 0.2</td>
</tr>
<tr>
<td>Neural component (NC)</td>
<td>NC was estimated at P2 (maximal extension at the end of the passive movement) by subtracting the elasticity (EC) and viscosity (VC) components from the total force.</td>
<td>NC = Total force_{P2} - (EC + VC)</td>
</tr>
</tbody>
</table>

3.7.2 Experimental setup

Passive extension of the wrist at controlled velocities was performed using a custom-built apparatus incorporating a computer-controlled step motor (Nanotec Electronic GmbH & Co KG, Landsham, Germany), performing the passive extension of the wrist (Figure 4A). The force and position during the testing session were sampled at 400 Hz, digitalized at 12-bit resolution and stored in SC/ZOOM (Department of Physiology, Umeå University, Sweden) for later analysis.

3.7.3 Nerve block paradigm

An ischemic nerve block test (Jaeger et al. 1982; Hayashi et al. 1987) was performed on a subgroup of the stroke subjects (n=7) in order to see whether the neural component was abolished or reduced, and also whether there is any correlation between the neural component and the amplitude of the EMG signals of the target muscle. A blood pressure cuff was placed around the subject’s upper arm and inflated to a pressure exceeding the systolic blood pressure with 30 mm Hg over 25 minutes. The cuff was first inflated for 25 minutes (T0-T25) and then the pressure was released over ten minutes (T25-
T35). The resisting force and EMG were measured during passive muscle stretch before inflation (T0) and every five minutes until the cuff was completely released (T35). The efficacy of the nerve block was clinically assessed after each measurement (T0 – T35) using the Fügl-Meyer scale (Fugl-Meyer et al. 1975).

Figure 4: (A) Hand, fingers, and forearm were fastened to the platform of a custom-built device that passively extended the wrist joint (50°) at controlled velocities (step motor). A force sensor was attached to the device under the hand in order to measure the total resisting force opposing the passive wrist movement. Surface electromyography (EMG) electrodes were placed above the belly of the flexor carpi radialis muscle (FCR). (B) Original trajectories of the total resisting force, EMG recordings, and the position of the hand are displayed during slow (5°/s) and fast (236°/s) extension of the wrist. Note that only the fast movement resulted in muscle activity. (C) A schematic illustration of the major components that contributed to the total passive resisting force trajectory. The black line illustrates the total force at 5°/s and 236°/s. During the slow movement (5°/s), the elasticity (purple) and the end range stiffness (gray) constitute the major contribution to the total force (P3), except for a minimal acceleration peak at the beginning of the movement. At faster speeds (236°/s), the first force peak (P1) occurring at about 15 ms after movement onset is composed of inertia (IC; dark blue) and viscosity (VC; light blue) forces. The later force peak at the end of the movement (P2) consists of viscosity (VC), elasticity and end range stiffness (EC), and the neural component (NC; yellow) from the stretch reflex (mV = millivolts; N = newton; ms = milliseconds).
3.7.4 Electromyography (EMG) recording and analysis

Bipolar circular Ag-Ag Chloride surface EMG electrodes (MYO 115, Liberty Technology, Hopkinton, MA, USA) were placed on the muscle belly of the flexor carpi radialis (FCR). The ground electrode was placed on the bony prominence of the ipsilateral olecranon process. While an active wrist movement was performed, EMG activities were observed simultaneously. EMG signals were sampled at 800 Hz and data were converted to root mean square with a 3 ms moving-window averaging technique (Hedberg et al. 2004). Rectified EMG was integrated during passive movement (from the onset of movement until the wrist is fully extended, 0-211 ms) and the area under the curve was quantified in millivolts (mVs).

3.8 STATISTICS

A variety of statistical methods were used in different studies. An overview is given in Table 5. Descriptions of the individual studies are given below.

Study I

Basic descriptive statistics were done to describe the demography. While reporting mean latency and amplitude of motor evoked potentials in TMS, the mean of three reproducible MEP is reported. The Spearman’s rank correlation test was used to explore associations between the different assessments, e.g., B&B, AHA. The level of statistical significance was set at \( p<0.05 \).

Study II

Descriptive statistics were produced. Further analyses were performed using the nonparametric tests. The Wilcoxon test was carried out to compare performance before and after CIMT (dependent samples) and the Mann-Whitney \( U \) test was carried out for intergroup comparison, e.g., to compare between different TMS projection patterns and brain lesion characteristics (independent samples) of outcome in mixed and ipsilateral projection pattern groups. For analysis of correlation, Spearman’s rho was used. The level of statistical significance was set at \( p<0.05 \).

Study III

Mean values from ten trials for the temporal and force parameters in each hand were calculated for each participant. Within hand differences and differences between participants with unilateral CP and typically developing
participants were determined using a 2 x 2 mixed model analysis of variance (ANOVA). The homogeneity of variance between groups was tested using Levene’s test. Pearson’s product-moment correlation test was performed to test for correlation between qualitative data, for example temporal parameters, grip force parameters, measures of mirroring activity and clinical data. Statistical significance was set at p<0.05.

Study IV

Nonparametric statistical tests were used throughout the study. Friedman analysis of variance (ANOVA) was used to assess velocity-dependent differences. For post hoc analysis and for within-group analysis, the Wilcoxon matched pairs test was used. For between-group analyses, the Mann-Whitney U test was used. The Spearman’s rank correlation test was used for correlations. Statistical tests were considered significant if p<0.05.

Table 5: An overview of statistical methods used in four studies of the thesis

<table>
<thead>
<tr>
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<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
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<tbody>
<tr>
<td>Descriptive statistics</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spearman’s correlation</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>Wilcoxon signed rank test</td>
<td></td>
<td></td>
<td>x</td>
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<tr>
<td>Mann-Whitney U test</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Leven’s test of homogeneity</td>
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<td>x</td>
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<tr>
<td>Pearson’s product-moment correlation</td>
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<tr>
<td>Mixed model repeated measure ANOVA</td>
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<td>Friedman’s ANOVA</td>
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3.9 ETHICAL CONSIDERATIONS

Informed written consents were obtained from participants/participating families or caregivers (where appropriate). Studies were approved by the regional ethics committee for Stockholm in accordance with ethical standards on human experimentation and the Helsinki Declaration of 1975, as revised in 1983.
4 SUMMARY OF RESULTS

4.1 STUDY I

Children with contralateral motor projections to their paretic hand showed better performance in the Box and Blocks (Figure 5) test and AHA (Table II, paper I) (Holmström et al. 2010), than those with ipsilateral corticomotor-projections.

A large spectrum of brain abnormalities was observed on MRI (Figure 6), including WMDI (n=10), focal infarction (n=4), and maldevelopment (n=2). Reductions in the size of the basal ganglia or thalamus were observed (using visual assessment) in the context of WMDI (n=4), focal infarct (n=2), and maldevelopment (n=2).

Patterns of motor projection to the paretic hand were contralateral (n=5), ipsilateral (n=5), or mixed (n=6). In the group with WMDI, all children with contralateral motor-projection patterns had mild or moderate white-matter loss, whereas all children with ipsilateral projections had severe white-matter loss (Table II, paper I) (Holmström et al. 2010).

![Figure 5: Relationship between the number of blocks moved in 60 seconds using the paretic hand (Box and Blocks test; y axis) and the motor-projection pattern (x axis)](image-url)
Figure 6: Axial slices showing each participant’s lesion on T2-weighed magnetic resonance imaging. (No MRI was available for participant 8.)
Figure 7: Chart showing individual changes in (A) Jebsen-Taylor hand function test (JTHFT); (B) Melbourne assessment (C) assisting hand assessment. Participants are grouped according to their motor-projection pattern as assessed with transcranial magnetic stimulation (TMS), i.e., contralateral (black bar); mixed (white bar) and ipsilateral (striped bar). Individual ID numbers are reported on the x axis.
4.2 STUDY II

Only two participants had typical contralateral projection as determined with TMS. The rest had either mixed (n=5) or ipsilateral (n=6) corticomotor-projection (Figure 7). The outcome of training was not significantly influenced by the organization of the projection pattern. There was however a trend of positive change in JTHFT for children in ipsilateral group (Figure 7A).

The basic patterns of damage were WMDI (n=9), focal infarct (n=3) and maldevelopment (n=2). The children without involvement in central nuclei or only thalamic involvement (n=7) improved more, in contrast to the children who had concurrent involvement of the thalamus and the basal ganglia (Figure 2, paper II, Islam et al. 2012).

There were no/weak correlations between changes in outcomes in three hand function assessments, although some correlations were found between assessments i.e. before the training (Spearman’s rho=-0.59 for JTHFT and AHA, and Spearman’s rho=0.67 for AHA and Melbourne Assessment).

Overall, we found that individual children improved to different extents, irrespective of their corticomotor-projection pattern and brain lesion. As a group, the children showed significant improvements in both JTHFT and AHA. However, not all children improved in all assessments.
4.3 STUDY III

Our finding shows that individuals with unilateral CP use a coordination pattern during bimanual manipulation that is different to that of typically developing individuals, in regards to both temporal coordination and control of the fingertip force amplitudes.

Temporal coordination between two hands is described schematically in Figure 8, which shows that typically developing participants (Figure 8A) started the task by increasing grip force in the holding hand (white bar), before the releasing hand started to release (black bar). This means that they had longer time to prepare the holding hand for the weight of the small device. Typically developing participants also completed the task smoothly over a longer period of time (striped bar). In contrast, the participants with CP (Figure 8B) started the task with releasing the small device (black bar) and showed that they could not anticipate the forthcoming weight from the other hand and ended up having very short preparation time (white bar). Moreover, in participants with CP, the time taken for releasing the device (striped bar) is also very short, indicating a relatively abrupt release. These differences were most prominent when the paretic hand served as the releasing hand.

In addition, the fingertip force generated by participants with unilateral CP in both preparation and the transition phase were smaller than the typically developing participants, resulting in a significantly smaller total grip force increase (Figure 2C, paper III) (Islam et al. 2011).

While investigating the existence of mirror movements (MM) in participants with unilateral CP, we found stronger MM in the non-paretic hand, but there was no significant correlation between the quantitatively measured mirror movements and any of the temporal or force parameters measured in the bimanual task or clinical assessments.
Figure 8: Schematic diagram (modified from Figure 2 A,B, paper III. Islam et al., 2011), showing an overview of coordination patterns between the releasing hand with the smaller device (top) and the holding hand with the larger device (bottom). This example illustrates non-dominant hand releasing and dominant hand holding in typically developing participants (A), and paretic hand releasing and non-paretic holding in participants with unilateral CP (B). “0” on the x axis is the point of contact between two devices. Releasing hand preparation time (black bar), holding hand preparation time (white bar) and transition phase (striped bar).
4.4 STUDY IV

In this study our aim was to develop a method that can measure different components of spasticity and to validate the model. The model was validated in three ways:

a) Whether NC was reduced after an ischemic nerve block

The model could measure the reduced neural component (NC) after an ischemic nerve block (Figure 9A). NC decreased over time and at after 25 minutes (T25) the nerve signals in large afferents were blocked significantly as compared to T0 (p<0.05), which was confirmed clinically as patients could not discriminate between sharp and dull sensation on skin at T25.

b) Whether changes in NC correlated with the integrated EMG

Correlation between NC and EMG activity was shown in two ways.

(1) After an ischemic nerve block, the changes in NC (Figure 9A) correlated significantly with simultaneous changes in integrated EMG of the FCR muscle (Figure 9B) ($\rho=0.86$, $p=0.007$).

(2) The decrease in NC correlated significantly with the decrease in muscle activity in all three velocities across subjects ($r = .62$, $P < .001$ at 71°/s; $r = .58$, $P < .001$ at 142°/s; $r = .64$, $P < .001$ at 236°/s) (See also Figure 3, paper IV) (Lindberg et al. 2011).

c) Whether NC was velocity dependent

There was a significant increase in NC with increased velocity (Figure 9C) and integrated EMG also showed a velocity-dependent increase (Figure 9D). Both NC and EMG changes were evident in stroke patients but not in the control subjects. (See also Figure 4A, paper IV, Lindberg et al., 2011.)

Correlation with modifies Ashworth scale (AS)

We also found strong positive correlation between the Ashworth score and both NC and total force across velocities ($r > .6$, $P < .001$).
Figure 9: Velocity-dependent modulation of the forces that resist the passive muscle stretch in stroke patients and control subjects. A) the neural component (NC) and B) the EMG of the FCR muscle during the ischemic nerve block test in five patients with complete nerve block. The median and quartile range are indicated. The grey shaded areas mark when the blood cuff was inflated above the systolic blood pressure, C) the neural component at the three different velocities and D) the integrated EMG are shown at the three velocities in patients with stroke (S) and control (C). Squares and whiskers show the median and quartile ranges 25% to 75%. (N-newton).
5 GENERAL DISCUSSIONS

In this thesis, there is some heterogeneity in participating groups, research questions and methodological approaches within studies. This gave us a broad overview of different aspects of hand function from the points of unilateral brain lesions and plasticity of the central nervous system. The discussions below aim to highlight those issues.

5.1 SENSORIMOTOR REORGANIZATION AND HAND FUNCTION

We have investigated the relationship between hand function, brain lesions, and corticomotor-projection in Study I. Our results show that the most favorable hand function was present in children who had contralateral motor projections and white-matter damage of immaturity with mild white-matter loss. Since the initial work of Carr et al. (1993), many studies have used TMS to determine corticomotor projections and as expected have correlated the contralateral pattern with better hand function. At the same time, an ipsilateral projection from the unaffected hemisphere to the paretic hand is frequently identified, which has been associated with poor hand function (Carr et al. 1993; Carr 1996; Thickbroom et al. 2001; Staudt et al. 2002; Vandermeeren et al. 2003b). In that context, an interesting observation of our study is that, in a subgroup of children who had ipsilateral corticomotor-projection from the unaffected cortex, we found fairly good hand function on the paretic side. This was illustrated by a wide range of AHA scores, indicating a rather well functioning assisting hand in some of the children within this projection pattern group (Table 2, paper I) (Holmström et al. 2010). It is uncertain whether this reflects typical development or an effect of a long-term treatment program. However, this finding is in line with our results in Study II, where we further show that the children with ipsilateral projection also have the potential to benefit from constraint-induced movement therapy. Although the ipsilateral corticomotor-projection following a lesion to the immature brain is likely to be a compensatory effort by the nervous system to preserve hand function, apparently this does not compensate for the neuronal damage sufficiently to restore adequate hand function. As described in the introduction, it has been argued that the reorganized ipsilateral corticomotor-projection could be a result of an activity-dependent competitive withdrawal of contralateral projection rather than a compensatory reparative mechanism (Eyre et al. 2007a; Eyre 2007b). The possibility of a difference in the functional connectivity between ipsilateral and contralateral projection can be discussed further. We have reported one child in Study II, in whom the scalp location of the ipsilateral
and contralateral projection was same, but a higher stimulator output was needed to generate an ipsilateral MEP, indicating a lower excitability of the ipsilateral projection innervating paretic upper limb. Maegaki and colleagues reported a distance of 1-2 cm between the scalp positions for ipsilateral and contralateral responses from the unaffected hemisphere (Maegaki et al. 1997). In another recent study, results from MRI guided TMS showed evidence of reorganization of hand representation in unaffected hemisphere, since the cortical origin of ipsilateral projection was found more caudal to the hand motor area. These results possibly reflect an activity dependent reorganization of corticomotor-projection (Vandermeeren et al. 2009).

Our finding that, better hand function was seen in children with mixed projection than in those with ipsilateral, could be attributed to the fact that, ipsilateral corticomotor-projection is generally associated with more severe brain abnormalities (Staudt et al. 2002; Vandermeeren et al. 2003a). Both in Studies I and II, we have identified a spectrum of brain abnormalities that included WMDI, focal infarcts and maldevelopment. In addition, lesions in basal ganglia irrespective of whether the primary lesion was in periventricular white matter or in cortical grey matter were predominant in children with ipsilateral motor projection. Forssberg et al., 1999 showed correlation between the grip-lift synergy to the total extent of lesions in the contralateral hemisphere, white matter lesion and with lesions in the thalamus/basal ganglia (Forssberg et al. 1999). The relationship between the involvement of central nuclei (BG, thalamus) and the outcome of CIMT has been investigated in Study II.

The term sensorimotor reorganization has been used in this thesis and the terminology refers to reorganization of somatosensory pathways, in addition to the motor system. Although we have not investigated reorganization of sensory tract, clinical assessment of sensory function shows that, children with ipsilateral projection are also presented with poor sensory function (see table II, Study I) (Holmström et al. 2010). Sensorimotor integration is necessary for skillful hand movements. Inter-hemispheric dissociation, i.e., ipsilaterally reorganized corticomotor-projection but contralaterally preserved sensory afferent, could be a contributing factor to impaired sensorimotor integration and the poorer functional outcome in children with unilateral brain lesion (Staudt et al. 2006; Guzzetta et al. 2007).

We have investigated the role of mirror movements on hand function in Studies I and III. We were unable to establish any clear correlation between MM and AHA or box and blocks test (study I) or asymmetric bimanual task (study III). The neurophysiology behind MM is outlined in the introduction.
Symmetrical unintentional mirror movements are likely to interfere with asymmetric bimanual actions, but some participants with very strong mirror movements could still complete the task in Study III. One possible explanation could be that some children are able to suppress MM to an extent, which allowed them to complete the bimanual task. A similar strategy of suppressing MM has been reported earlier (Kuhtz-Buschbeck et al. 2000). Association of MM with reorganized corticospinal projection is also described in previous studies (Carr et al. 1993; Maegaki et al. 1995; Vandermeeren et al. 2003a). Unfortunately, we do not have information about corticomotor-projection in participants for Study III. That could give us additional insight into the correlation between reorganized corticomotor-projection, extent of MM and asymmetric bimanual task.

It has been discussed in previous studies, whether reorganization is a form compensatory alternation of an existing neural network or a response to lesions in the developing brain altering the normal trajectory of ongoing development (Muller et al. 1997; Eyre et al. 2001; Eyre et al. 2007a; Staudt 2010a; Cioni et al. 2011). However, as far as clinical implication is concerned, our concluding remark is that a combination of neurophysiological method and good neuroimaging data can better describe hand function at an early age.

5.2 CIMT IN RELATION TO CNS PLASTICITY AND BRAIN LESIONS

The overall aim of Study II was to explore individual variation in outcome after CIMT relation to corticomotor-projections and lesion characteristics in unilateral CP. Our findings show that children with unilateral CP have the potential to achieve improvement to a different extent, in all three corticomotor-projection patterns.

Our results differ to some extent from previously published data by Kuhunke et al., who raised the hypothesis in the first place (Kuhunke et al. 2008). The authors compared contralateral and ipsilateral motor projection in relation to the outcome of CIMT and reported that children with contralateral but not ipsilateral corticomotor-projection showed improvement in the Wolf motor function test, which measured their gain in speed and quality of movement. In our study, we have identified all three basic patterns of corticomotor-projection and also found that children with ipsilateral projection patterns have the potential to benefit from CIMT. Interestingly, five out of six children with ipsilateral projection in our study showed a positive change in JTHFT (Figure 7A). Two main arguments submitted by Kuhunke and coauthors against the possibility of the ipsilateral group for improving through CIMT are (a) an
imbalance in transcallosal inhibitions (Hummel and Cohen 2006), and b) interhemispheric dissociation (Staudt et al. 2006), which nevertheless are widely accepted consequences of unilateral brain lesion. Why there would be variations in outcome after intensive training in children with similar corticomotor projections cannot be readily explained, but is can be discussed. The characteristics of brain lesions are fairly heterogeneous within the group of ipsilateral projection. Thus, the effect of projection pattern on training outcome could be further influenced by different in underlying brain lesions in individual level and not showing any causal relationship. In children with ipsilateral projection, motor presentation for both hands are located in same hemisphere, but whether the amount of interhemispheric imbalance and its influence would be same in all participants is not very well understood. Especially in cases of CIMT when the paretic hand receives motor projection from the unaffected hemisphere and the non-paretic hand is restrained. In children with unilateral brain lesions, the activity of the undamaged neural circuit might be different due to the fact that their upper limb is used less or is used in an atypical way. It is true that the interhemispheric dissociation and impairments in sensorimotor integration are interrelated, but such dissociation might not be consistently present in all children with unilateral brain lesion. In a recent study in children with unilateral CP reported an alteration of evoked responses in magnetoencephalography (MEG) in both hemispheres after median nerve stimulation of the paretic hand (Nevalainen et al. 2012). This result raises the possibility of an alternative explanation than predicting obvious “interhemispheric dissociation” in all children with unilateral CP.

The effect of brain lesions on hand function and general motor ability is outlined in the introduction. In our study, children responded to CIMT to various extents irrespective of their lesion type, location and extent. The only trend of association we could find was the role of involvement of central nuclei. We found that children with involvement with only basal ganglia responded better to CIMT, compared to when both basal ganglia and thalamus were involved. The role of the basal ganglia and the thalamus in the development of hand function is discussed in previous literature (Feys et al. 2010; Holmefur et al. 2012). In order to obtain a clear insight into the correlation between involvements of central nuclei and outcome after intensive training, further studies are required including larger and more heterogeneous samples.

One intriguing finding of our study was the individual variation in outcome depending on the assessment chosen. Although the baseline scores in all three assessments had fairly good correlation between them, their outcomes were largely divergent. The results suggest that different assessments would capture
different aspects of improvement (if any). Studies investigating the outcome of CIMT tend to use wide varieties of assessment tools that are not consistent between studies. This could be a contributing factor for large inter-individual variations in reported outcome of CIMT. The contribution of various other factors such as the initial degree of motor impairment, age, cognitive ability and other additional impairments to the large inter-individual variations in the outcome of CIMT has been discussed in previous studies, but a causal relationship is not well established between factors and outcome (Charles and Gordon 2005; Hoare et al. 2007). This needs to be further investigated in larger trials including participants with different motor projection patterns as well as brain lesion types.

### 5.3 ANTICIPATION DURING AN ASYMMETRIC BIMANUAL TASK

The results from Study III show that, participants with unilateral CP had grip force increase in the holding hand after the releasing hand grip force had started to decrease (Figure 8B), which was opposite to the pattern in case of typically developing participants (Figure 8A). Disturbed temporal coordination of bimanual movements has been reported earlier in children with unilateral CP (Bleyenheuft and Thonnard 2010; Hung et al. 2010), but the interesting part our findings are in that, the study participants were not only late to start increasing holding hand grip force, but also released the device fairly quickly after the point of contact between devices. This abrupt release indicates the difference of control in the asymmetric task compared with the typically developing participants.

We also find it remarkable that there was no “catch-up” in grip force generation after the point of contact, even when the non‐paretic hand was acting as the holding hand. Apparently the paretic hand interferes with the subsequent force adjustments in the non‐paretic hand. Hence, the unexpected finding of our study was the poor performance of the non‐paretic hand. As reported previously, during an asymmetric bimanual task, the non‐paretic hand might not serve as a template for the paretic hand since two limbs require decoupling to act independently (Gordon and Duff 1999; Eliasson and Gordon 2000). In another experiment, Volman and colleagues asked children with unilateral CP to draw circles using two hands and also showed increased temporal and spatial variability during drawing in an asymmetric coordination mode (Volman et al. 2002).

It is possible that changes in the neural circuitry after an injury to the central nervous system would result in disturbed temporal coordination and impaired
force scaling during asymmetric bimanual activity. Based on a similar bimanual (un)loading task, Massion et al. (Massion et al. 1999) suggested two independent controllers, i.e., one neural circuit controlling the voluntary load-lifting movement (object releasing hand in this study), and another circuit controlling the anticipatory adjustment compensating for the load change in the other hand/arm. The two circuits were proposed to be coordinated by a common timing signal. This model could be adapted for the paradigm of Study III. Independent circuits for each hand control the fingertip forces that are accurately changed in opposite directions, while the temporal coordination of the motor activity of the two hands is disturbed. This would mean that the neural network responsible for the timing of the two different motor circuits is impaired. The location of such a coordinating network is not clearly known, but it might require sensorimotor areas in both hemispheres (distributed network). As outlined in the introduction, it is possible that lower force generation in the paretic hand might not only be a result of poor motor output from M1, but also because of the lack in other brain areas, e.g., SMA (Wiesendanger and Serrien 2004) and basal ganglia (Forssberg et al. 1999), involved in controlling the motor signals between hands.

Planning bimanual activities in unilateral CP may involve more factors in addition to just executing a simple motor command. Sköld and coworkers (2004) suggested that factors such as feasibility of success, social aspect and ability to tolerate negative consequence of the action are also important for planning bimanual tasks. Children with unilateral CP would perhaps a need for extra time, planning, or concentration in order to perform desired bimanual activities (Sköld et al. 2004), either symmetric or asymmetric.

5.4 MEASURING SPASTICITY: A CLINICAL CHALLENGE

The influence of spasticity on motor impairments and activity limitation is very difficult to assess, since the degree of spasticity changes according to the position of the subject and the task being performed (Sommerfeld et al. 2004). It is both crucial and difficult to have a reliable measurement of spasticity in a clinical setting. As outlined in the introduction, passive movement resistance that is measured using the Ashworth scale is the summation of the physiological changes in spasticity. The results from Study IV validate the proposed biomechanical model and suggest that it could separate the neural from the non-neural components. However, our model is validated in adults with stroke. Since the possible neural mechanism of spasticity is likely to be similar in children and adults, examples from both age groups are discussed where appropriate.
Evidence of validity

In line with Lance’s definition (Lance 1980), previous studies have shown that NC is velocity dependent (Powers et al. 1988). Ibrahim and colleagues studied stretch-evoked EMG activity in patients with spastic hemiparesis and showed that the duration of EMG response was dependent on the stretch velocity during passive movement (Ibrahim et al. 1993). In our study, the hand was passively moved at different velocities (71°/s, 142°/s and 236°/s), with an expectation that the NC would be larger with increasing speed of the passive stretch. The velocity-dependent changes could be seen only in subjects with stroke and not in healthy controls, which further validated the model (Figures 9C, 9D). Most importantly, after an ischemic nerve block (Hayashi et al. 1987) there was a reduction of NC over time (Figure 9A), and this was further validated by concurrent changes in EMG (Figure 9B).

The model could measure the increase in both viscosity (VC) and elasticity (EC) that quantified the mechanical properties of spasticity. The increased resistance is known to be contributed by the altered property of the muscles and the stretching of connective tissue. Recent examinations of spastic muscle changes have shown increased passive resistance in type 2 muscle fibers and in titin, an important muscle protein for resting tension and elasticity (Olsson et al. 2006). The proportion between type 1 and type 2 muscle fibers may be altered after stroke (Dattola et al. 1993), which may explain the small net increase in elasticity. A decrease in size of spastic muscle together with a concurrent increase in extracellular matrix has been reported, which serves as an explanation why, in our patients, VC was consistently smaller than in controls (Lieber et al. 2003).

Clinical assessment using the Ashworth scale

The most commonly used assessment of spasticity is the Ashworth scale (AS) and the validity and reliability of this method has long been debated (Ansari et al. 2006; Alibiglou et al. 2008). The AS is easier to use in a clinical setting, but it cannot capture the complex picture as presented with spasticity (Hobart et al. 2007). From our results, it could be shown that the same levels of spasticity in two different subjects were not contributed equally by neural and non-neural components (for example, see values from S2, S16 and S7 in Figure 5 , Study IV) (Lindberg et al. 2011). This means that with a subjective measure like AS, a patient with high NC can be misinterpreted and selected for treatment with muscle stretching exercises, whereas the patient should have been considered for therapies aimed at reducing the exaggerated spinal reflex, or vice versa.
Emerging treatment options such as Botulinum toxin injection, intrathecal baclofen or contralesional repetitive transcranial magnetic stimulation, are all aimed at reducing the neural component of spasticity. In these cases, the subjective measure using the Ashworth scale would certainly give very limited clinical information.

**Neurophysiology of spasticity and possible functional plasticity**

Spasticity is a spinal phenomenon which has been explained as a consequence of the imbalance between excitatory and inhibitory signals from the supraspinal nuclei (Nielsen et al. 2007). In addition, after any unilateral brain lesion, there is also an imbalance in transcallosal inhibitions, where the unaffected hemisphere tends to overpower activity of affected hemisphere (Ferbert et al. 1992; Kobayashi et al. 2004; Murase et al. 2004; Nowak et al. 2009). In an fMRI study Lindberg and colleagues showed velocity dependent increase of activity in both contralateral and ipsilateral sensorimotor cortex during slow and fast passive movements of the hand. Results from that study further emphasized the possibility of involvement of ipsilateral sensory and motor cortex in generating spasticity after stroke (Lindberg et al. 2009).

Now there are growing numbers of studies, showing that the application of inhibitory (1 Hz) repetitive TMS (rTMS) of unaffected hemisphere can result in suppression of excessive transcallosal inhibitions towards the affected hemisphere and improve hand function in adults with stroke (Mansur et al. 2005; Mally and Dinya 2008) and children with unilateral CP (Valero-Cabre et al. 2001). The therapeutic uses of contralesional inhibitory rTMS increases cortical excitability of the affected hemisphere and further modulate the synaptic transmission in corticomotor pathway (Nowak et al. 2009). In case of spasticity it would be relevant to assess the expected change in neural component (reflex arc) to measure the clinical outcome and also in order to understand circuitry better. In such cases, a subjective measure of spasticity i.e., the Ashworth scale will possibly hinder the outcome (if any). A quantitative measurement of changes in spasticity after rTMS would significantly increase our understanding of neurophysiological modification and the extent of functional plasticity.
5.5 METHODOLOGICAL CONSIDERATIONS

**Sample size**

The sample size in Studies I, II and III, which include children with unilateral CP, can be considered small and we acknowledge this. Even though it is challenging to draw any concrete conclusion from studies with smaller samples, we still believe that the children participating in our studies are representative of the clinical sample that is typically seen in neuro rehabilitation clinics or included in intensive training. The participants in Studies I and II exhibited a wide spectrum of brain lesion characteristics, and we were also able to identify all three patterns of corticomotor organization.

In Study II we invited 26 participants to be screened for TMS and MR investigation, and we could only include 16 in our final analysis. For Study III, 20 children with unilateral CP participated in data collection, whereas final analysis could only be carried out on 12 participants. This gives an overall idea of how difficult it is to recruit a larger sample, while working with pediatric populations.

**Methodological constrains of using TMS in children**

From available data in published studies, single pulse TMS is considered to be very safe as a method (Frye et al. 2008). However, the tolerability and compliance in case of children for participating in an extensive TMS session would vary widely among individuals and unpredictable at the same time. Thus extra precautions are to be taken while performing this method on children with existing functional disabilities. From our experience of using TMS in Studies I and II, it can be inferred that single pulse TMS is very well tolerated in children and adolescents. The youngest we have studied was a seven-year-old boy in Study I (participant no. 10). In order to make the TMS session more tolerable and increase cooperation, we modified our protocol so that it took fewer stimulations and less time to complete data collection, while still ensuring that we acquired sufficient information to answer our research question. Such deviations from standard protocols have been used and discussed previously for increasing participant cooperation (Staudt et al. 2004b). The methodological advantage in Study II allowed us to record MEP from two hands at the same time, which in practice decreased the duration of the experiment significantly (Table 3). Studies were conducted in the vicinity of a core hospital facility, where the same TMS setup is used in routine clinical investigations.
In our studies, the positioning of the TMS coil was not guided by MRI navigation. For an initial guideline, the primary motor cortex (M1) was marked on the scalp surface using the international 10-20 method. In the pathologic brain, however, it is possible that some extent of anatomical plasticity may have occurred or the normal anatomy is distorted by the extent of lesion. In any of these cases, the coil positioning will not be optimal to begin with and the specific area being investigated just beneath the TMS coil will as remain a question. Moreover, it is true that both the position and the angle of the stimulating coil could influence the variation in size and latency of the MEP significantly. The eddy current that the coil produces within the cortical neurons lies is parallel to the coil surface (Figure 2), and the neuronal population activated by TMS is highly dependent on the direction of the induced current in the brain (Mills et al. 1992; Rothwell et al. 1999; Terao and Ugawa 2002; Chen et al. 2003). With non-navigated TMS it is more difficult to be consistent in maintaining the location and the angle of the coil to reproduce MEP.

**Task complexity**

The task included in Study III was a fairly complex and novel task where the children had to generate an opposite pattern of finger tip grip force in two hands to complete the task. Moreover, the task required changes in finger tip grip force, simultaneously in both hands, forcing them to work against the effects of mirror movements, if present. As mentioned above, we had to exclude eight children from the final data analysis, which was largely because they could not deal with the complexity of the task. They either did not complete all the trials or in some cases even dropped the devices.

**Biomechanical model**

In Study IV we used a custom-built prototype for the biomechanical model, which has been used previously in functional imaging study and is described in details (Lindberg et al. 2009). The platform where the hand is placed is prepared to suit the cubital angle of the right upper limb, and for that reason we only recruited participants with right-sided hemiplegia. Certain amounts of error in estimation are likely, depending on the position of the hand on the platform, when the center of mass of the hand does not fall directly on the force sensor or if there is a slight misalignment of the wrist joint with the axis of rotation of the hand apparatus. Both fast and slow movement of the hand platform was well tolerated in all patients, irrespective of the level of spasticity.
Choosing the right assessment

As discussed already in this thesis, the mechanisms behind skillful hand movements are rather complex and the quality of hand function can depend on various intra and/or inter-individual factors. There are increasing numbers of studies with diverse research questions that concern assessment of hand functions. The ultimate goal with the accumulated results from these studies is however to add more to our existing knowledge on how to improve therapeutic measures and functional outcome. Irrespective to the results achieved, inhomogeneous characteristics of participants or variations in the chosen assessment tools are likely to lead to divergent and rather incomparable results among studies. Different aspects of the hand function can be captured depending on the assessment tools used for measurement. Although it is crucial to choose an assessment tool that can correctly measure hand function in response to a lesion or after therapeutic interventions, it is equally difficult to choose the right assessment for the right purpose. A quotation that justifies the statement is – “We sometimes measure what we measure because we can measure it... We do not measure what we should measure because it is more difficult and more complex. We then use the easy measure to infer things about the difficult measure.” (Simmonds 1997)
6  CONCLUSION AND CLINICAL IMPLICATIONS

In children with unilateral CP, despite having an ipsilateral corticomotor projection, it is possible to develop a fairly good hand function in the paretic upper extremity. Moreover, such reorganization of corticomotor projection does not limit the possibility of improving through CIMT. Combined neurophysiological and neuroimaging data can be used to predict hand function at an early age.

Bimanual hand function is frequently affected after unilateral brain lesions. Children with unilateral CP follow an alternative strategy in both fingertip force generation and temporal coordination, comparing typically developing children in order to overcome the complexity of asymmetric bimanual tasks. The ability of the non-paretic hand is affected by the activity of the paretic hand. Our findings may explain why children with unilateral CP sometimes prefer not to use the paretic hand during otherwise asymmetric bimanual tasks.

Spasticity is a clinical symptom that is commonly seen after lesions in the central nervous system. With our biomechanical model, it is possible to separate the neural component from mechanical contributions of spasticity and to quantify the symptom for direct clinical use.

The findings from this thesis are closely connected to clinical implications with increased understandings of (1) unimanual and bimanual hand function in response to unilateral brain lesion, (2) individual variations in outcome after intensive training to improve hand function, and (3) developing a method for the assessment of spasticity in clinical settings.
7 FUTURE DIRECTIONS

Most studies that have looked at sensorimotor reorganization in children with CP are cross-sectional studies. Getting a clearer concept of how the developing nervous system reacts to an early injury would require planning rather longitudinal studies. We will then be able to follow the development and change in the organization of corticomotor projections and relate these to their motor abilities and outcomes after training in that respect.

We have studied the possible impact of corticomotor reorganization on the outcome of CIMT. Such (re)organizations are not likely to be changed by intensive training. However, intensive training itself might induce intracortical reorganization in the form of expanding hand motor area or changes in intra- and inter-hemispheric inhibitions. This question needs to be further investigated in children with early brain lesions, to further improve our understanding of both the mechanism and the variations of outcome after intensive training.

Moreover, the use of repetitive TMS to achieve a balance in inter-hemispheric inhibition, in order to improve hand motor function and reduce spasticity, has not been thoroughly investigated in children with unilateral CP. Would suppressing the inhibition from the healthy hemisphere in children with unilateral CP a) facilitate plastic changes in the brain, b) decrease spasticity, and c) improve motor function?

The theoretical concept of separating different components of passive movement resistance has progressed from paper to product over the years. Based on the results validating the biomechanical model in adults with stroke, the model has already been developed into an apparatus, NeuroFlexor®, for use in purely clinical settings. The model is yet to be validated in children with cerebral palsy. The immediate future target is therefore to validate the model in pediatric populations.

With the availability of advanced neuroimaging (MRI, fMRI, DTI and PET) and neurophysiological modalities (TMS, navigated TMS, EEG and MEG), research should now focus on combining methods to a) improve our knowledge of sensorimotor reorganization, b) develop better tools for measuring clinical symptoms, and c) design more effective rehabilitation procedures.
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9 REFERENCES


