From THE DEPARTMENT OF
WOMEN'S AND CHILDREN'S HEALTH
Karolinska Institutet, Stockholm, Sweden

NEURAL CORRELATES OF HAND FUNCTION IN TYPICALLY DEVELOPING INDIVIDUALS AND CHILDREN WITH UNILATERAL CEREBRAL PALSY

Linda Holmström

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ABSTRACT

The ability to use our hands is crucial in order to achieve the goals of almost all activities in everyday life. Most of us learn how to handle objects and adjust our hand and finger movements to perform increasingly difficult tasks during childhood and adolescence. This is what is expected, but what happens to our hand motor skills when the motor system is damaged during development and things no longer go according to plan?
The motor cortex and corticospinal system are common sites of brain damage in the prenatal and perinatal period and it is well established that the corticospinal system has the capacity of substantial re-organization. One main focus of this thesis is how the underlying brain lesion and pattern of re-organization affects hand function in children with unilateral cerebral palsy (CP). A second focus of this thesis is the ability to use a precision grip during dexterous manipulation of unstable objects, both in adults and typically developing children.

The main aim of study I was to analyze the internal scale validity of the Strength–Dexterity Test (SD-test) in a typical pediatric population. This test that was developed to measure dynamic control of fingertip forces during grasping. In study II, items from the SD-test was used to study the neuroanatomical correlates of fingertip force vector direction and magnitude control in adults using functional magnetic resonance imaging (fMRI).
Study III and IV included children with unilateral CP. The aim of these studies was to investigate associations between hand function, brain lesion characteristics, and motor projection patterns using conventional structural magnetic resonance imaging (MRI), transcranial magnetic stimulation (TMS) (Study III) and diffusion tensor imaging study (IV).

The results from Study I show that the SD-test has internal scale validity when administered in a typically developing pediatric population. The SD-test measures a uniqe unidimensional latent trait that is likely to reflect individual differences in dynamic control of the fingertip force vectors. Study II confirms a recently described bilateral fronto-parieto-cerebellar network for manipulation of increasingly unstable objects. Dynamical control of fingertip force direction, was associated with activity in the bilateral precentral gyri, postcentral gyri/sulci at the level of the intraparietal sulci and bilaterally in the cerebellum (lobule VI), while fingertip force magnitude was related to unilateral activation of the (contra lateral) precentral gyrus and bilateral cerebellum.

The results from study III showed that motor projection patterns appeared to be influenced by lesion extent and location, but not by lesion type. The results also showed that children with ipsilateral projections can develop fairly good hand function and this has not previously been reported. The overall findings from study IV indicate that diffusion measures correlated with hand function in the non-dominant hand in children with unilateral CP, and that diffusion MRI provides additional information to visual analysis of conventional structural MRI about structural changes in corticofugal fibers in this group of children.

The overall clinical implications and conclusions from this thesis are that combined information from TMS, visual inspection of conventional structural MRI and the use of quantitative measures from diffusion MRI can improve our ability to predict hand function in children with unilateral CP. The SD-test, although still requiring further development to be a clinical useful tool, offers the possibility to, in a clinical setting, capture an important aspect of dexterous fine motor control. The SD-test also provides an interesting concept that can be used to study the neural correlates of dynamic control of fingertip forces.

LIST OF PUBLICATIONS

I. Vollmer B, Holmström L, Forsman L, Krumlinde-Sundholm L, Valero-Cuevas FJ, Forssberg H, Ullen F. Evidence of validity in a new method for measurement of dexterity in children and adolescents. Dev Med Child Neurol. 2010, 52(10):948-954.

II. Holmström L, de Manzano Ö, Vollmer B, Forsman L, Valero-Cuevas FJ, Ullén F, Forssberg H. Dissociation of brain areas associated with force production and stabilization during manipulation of unstable objects (Submitted).

III. Holmström L, Vollmer B, Tedroff K, Islam M, Persson JK, Kits A, Forssberg H, Eliasson AC. Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. Dev Med Child Neurol. 2010, 52(2):145-52.

IV. Holmström L*, Lennartsson F*, Eliasson A-C, Flodmark O, Clark C, Tedroff K, Forssberg H, Vollmer B. Diffusion MRI in corticofugal fibers correlates with hand function in unilateral cerebral palsy (Submitted).
* These authors contributed equally to this work

CONTENTS

LIST OF ABBREVIATIONS

AHA	Assisting Hand Assessment
AIP	Anterior intraparietal sulcus
B&B test	Box and Blocks test
BOLD	Blood oxygen level dependent
CIMT	Constraint induced movement therapy
CMA	Cingulate motor area
CP	Cerebral palsy
CST	Corticospinal tract
DTI	Diffusion tensor imaging
DWI	Diffusion weighted magnetic resonance imaging
FA	Fractional anisotropy
FDR	False discovery rate
FLAIR	Fluid attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GMFC	Gross Motor Function Classification System
M1	Primary motor area
MACS	Manual Ability Classification System
MD	Mean diffusivity
MEP	Motor evoked potential
MNI	Montréal Neurological Institute
MRI	Magnetic resonance imaging
PMD	Dorsal premotor area
PMV	Ventral premotor area
RF	Radio frequency
ROI	Region of interest
SD-test	Strength Dexterity Test
SMA	Supplementary motor area
TE	Echo time
TMS	Transcranial magnetic stimulation
TR	Repetition time
WMDI	White matter damage of immaturity
$(\lambda_2 + \lambda_3)/2$, $(D_\perp)$	"Radial diffusivity", mean diffusivity along the two minor axis
λ_1, $(D_{//})$	"Axial diffusivity", diffusivity along the principal axis

1 INTRODUCTION

The ability to use our hands is crucial in order to achieve the goals of almost all activities in everyday life. Many activities require that we are able to handle objects that are fragile and/or can change shape in response to compression forces, like an egg or the stem of a flower. This means that we risk to damage or break the object if the grip forces applied to the surface of the object are too high. If we consider the opposite, applying too little force so as to be on the safe side not to squeeze too hard, we risk that the object slips and is dropped. Manipulation of unstable objects stresses the demands on dynamic on-line adjustments of both direction and magnitude of fingertip forces and this ability is, although essential in many everyday tasks, not extensively studied to date.

Most of us learn how to handle objects and adjust our hand and finger movements to perform increasingly difficult tasks during childhood and adolescence. We start off with just simply grasping and holding things, for instance our own foot, a block of Lego or some other kind of toy. Gradually, our motor skills develop and improve, and we move on to more advanced manipulation tasks and activities, such as tying shoe laces or playing video games. We become more skillful with age and experience, and by the time we reach the end of adolescence we can do most everyday tasks with success and very little effort. This is what is expected, but what happens to our hand motor skills when the motor system is damaged during development and things no longer go according to plan?

The motor cortex and corticospinal system are common sites of brain damage in the prenatal and perinatal period and it is well established that the corticospinal system has the capacity of substantial re-organization (Carr 1996; Eyre et al. 2007; Thickbroom et al. 2001). One main focus of this thesis is to describe how the underlying brain lesion and pattern of re-organization affects hand function in children with unilateral cerebral palsy (CP). Specific features of the re-organization of the motor system in children with unilateral CP will be described later in this introduction. To give a background to this an overview of the anatomy and typical development of the corticospinal system will be outlined in the next section.

A second focus of this thesis is the ability to use a precision grip during dexterous manipulation of unstable objects, both in adults and typically developing children.
The developmental course of force control and the neural correlates of precision grasping of stable objects will be described in the subsequent sections of this introduction.

1.1 THE MOTOR SYSTEM, BRIEF OVERVIEW

Voluntary action, including skilled hand and finger movements rely on a number of brain regions that together with the motor pathways constitute the motor system; the motor cortex, basal ganglia, thalamus, midbrain, cerebellum and the spinal cord. The corticospinal tract (CST), originating from the primary motor cortex and projecting directly to neurons in the spinal cord, connects the components of the motor system (see Figure 1) and is crucial in hand movements and object manipulation (Kandel et al. 2000; Lemon and Griffiths 2005; Martin 2005).

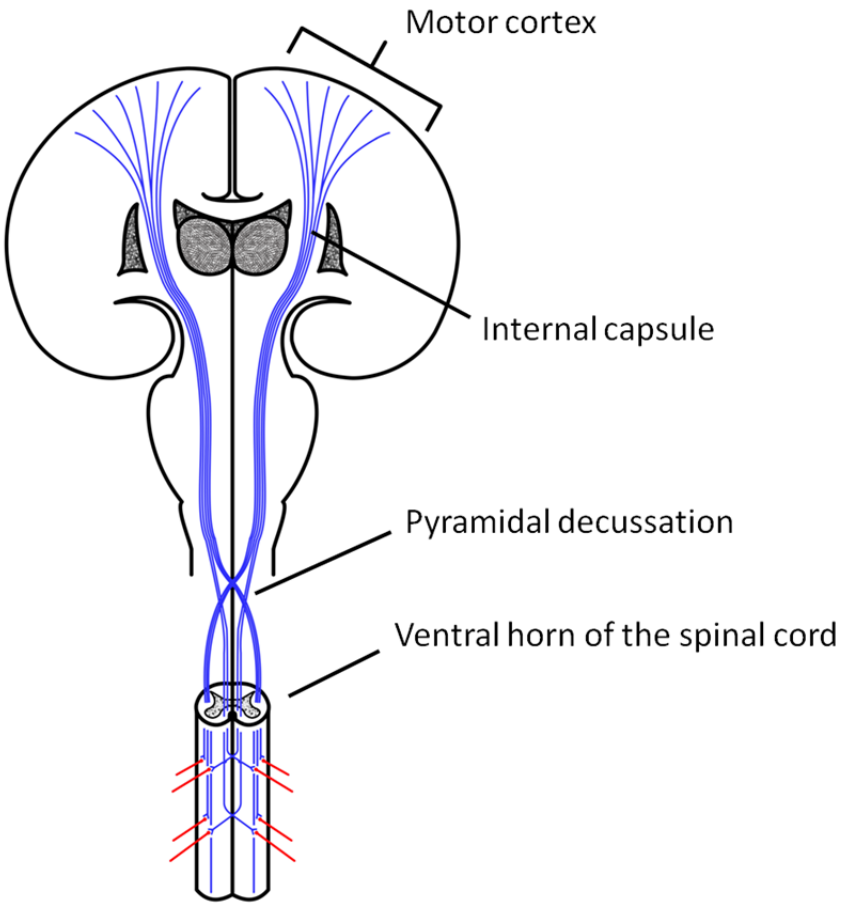


Figure 1. Schematic illustration of the descending fibers of the corticospinal tract

The axons of the tract descend through the internal capsule and cerebral peduncle, and most of the fibers cross at the pyramidal decussation on the way down to the end point in the ventral horn of the spinal cord. Movement commands initiated in the pre- and primary motor cortex travel through the CST and are continuously updated and modulated by tactile, visual and proprioceptive information from the other components of the motor system. The thalamus serves as a relay station, enhancing or preventing the passing of sensory information to the cerebral cortex. Information from the cerebellum and basal ganglia are essential for performance of smooth and well timed hand and finger movements (Prodoehl et al. 2009) and the nuclei in the thalamus that participate in motor functions transmit this information to the frontal motor regions (Kandel et al. 2000).

1.2 DEVELOPMENT OF THE CORTICOSPINAL SYSTEM

The corticospinal system is the last motor system to develop and there is a close relationship between maturation of the corticospinal system and improvements in fine motor skills. As described above the corticospinal neurons in the cortical motor area project to the spinal cord. There is a gradual increase in the number of axons that populate the tract (Martin 2005), and the axons reach the spinal cord no later than 24 weeks post conception (Eyre et al. 2000). Target-derived factors attract and guide the growing axons and a particular pattern of collateral branching constrains which spinal neurons the axon can engage (Martin 2005). The axons innervate the grey matter and begin to express neurofilaments and undergo myelination around the time of birth (Eyre 2003). A common feature of the corticospinal projection pattern early in development is that it is more extensive than in maturity (Martin 2005) and significant bilateral innervations of spinal motoneuronal pools from each motor cortex have been demonstrated in the newborn, resulting in both ipsi- and contralateral motor projections (Eyre 2007). Most of the ipsilateral projections can be expected to withdraw during the first two years of life in normal development (Eyre et al. 2001), and this phenomenon has been studied using transcranial magnetic stimulation (TMS). This method will be described in more detail in the methods section of this thesis. Persisting ipsilateral projections in older children and adults are reported to have a slow and small response when stimulated with TMS. Short latency ipsilateral responses do not occur beyond the perinatal period (Eyre 2003). The refinement and elimination of terminations is driven by neural activity in the motor cortical areas and by limb use (Martin 2005), and the withdrawal of the ipsilateral projections can be seen as the result of activity dependent competition for spinal synaptic space between the two hemispheres (Eyre 2003).

Typical development of the corticospinal system is crucial for the ability to perform advanced fine motor tasks later in life and these types of tasks often require the use of a precision grip. The developmental course of aspects of force control needed for successful manipulation of unstable objects using a precision grip and the neural correlates of the precision grip during object manipulation of will be described in the following sections.

1.3 THE PRECISION GRIP

The ability to use our hands in an efficient way is essential to most everyday tasks. The skills we need for successful performance in a specific situation is depending on a number of different contextual factors such as the complexity of the task, the constraints put on the task by the environment and whether the task requires completion within a given time frame. To grasp and manipulate an object in order to complete everyday tasks, we need to be able to handle objects with great precision and exactness. To do this, we often use a precision grip, i.e. a grip that involves the tips of the fingers.

Performance of a precision grip task is complex and involves different neural components e.g. sensory motor integration and visuo-motor control (Flanagan et al. 2006; Olivier et al. 2007). Johansson and Flanagan have shown that internal representations of object properties, such as, weight, shape and surface friction, are stored in the brain and used to program force output in advance. Sensory information is used to adjust the fingertip forces on-line, as well as to update the internal representation of the object (Johansson and Flanagan 2009). The memory representation, which enables prediction of future sensory events and execution of corrective movement commands in response to these during precision gripping is thought to depend on the formation of forward internal models (Flanagan et al. 2006; Flanagan and Wing 1997; Kawato 1999; Ohki et al. 2002).

The next section focuses on the development of force control during precision grasping since this ability is central to two of the studies included in this thesis. However, although not within the scope of this thesis, there are other important aspects of grasping such as appropriate selection of grip pattern, prehension and the ability to move the fingers independently.

1.3.1 Development of force control in precision grasping

Children start to move their hands and fingers to form grips already during the first months of life, and pre-precision grips associated with a variety in digit postures, precision grips including the pincer grasp, and self-directed grasps can be seen in infants between one and five months of age (Wallace and Whishaw 2003). When discussing the developmental course of different aspects of grasping and when during development a certain milestone should be met, it is important to note that up until school age typically developing children show large inter-individual variability in force control (Deutsch and Newell 2004), motor speed and overall performance of fine motor tasks (Gasser et al. 2010; Largo et al. 2001).

Development of grip strength is continuous throughout childhood (Smits-Engelsman et al. 2003) and correlations have been reported between grip strength and anthropometric measures (Hager-Ross and Rosblad 2002). The ability to adjust grip forces begins to develop at one to two years of age and gradually improves during childhood and adolescence (Eliasson et al. 1995a; Forssberg et al. 1992). At this early age, children tend to use a high safety margin, indicated by the use of a relatively wider grip (Kuhtz-Buschbeck et al. 1998) and excessive force to avoid slipping during grasping (Forssberg et al. 1995). Interestingly, children before the age of 3 do not seem to use visual size information during force programming (Gordon et al. 1992) and young children also overshoot and use of too much force in visuomotor force control tasks (Blank et al. 2000; Potter et al. 2006). The ability to maintain a certain force level during this type of task does not become stabile until the age of 8-10 years, when a general decrease in movement variability also is seen (Deutsch and Newell 2002; Deutsch and Newell 2004).

Young children depend largely on sensory motor feedback during grasping. However, a shift towards an integrated feedback and feedforward control during lifting with a precision grip gradually evolves during development (Blank et al. 2000; Forssberg et al. 1991). The use of anticipatory control strategies, i.e. the use of information on object weight, shape and surface, obtained from a previous lift, starts to develop around the age of two years and continues to improve during childhood until the early teen years (Eliasson et al. 1995a; Forssberg et al. 1992).

Boys and girls generally follow the same developmental course when it comes to aspects of hand function and very few sex differences are seen in performance of fine motor tasks during childhood (Gasser et al. 2010; Largo et al. 2001). This also holds true for the initial development of grip strength which is parallel for boys and girls up until the age of 9-12 years. However, boys can be expected to be stronger after this age (Hager-Ross and Rosblad 2002). The next section will describe the neural correlates of precision grasping in adults.

1.3.2 Neural correlates of the precision grip

The availability of imaging techniques such as functional magnetic resonance imaging (fMRI) has made it possible to map the network of brain regions that show increased blood-oxygen-level-dependent (BOLD) activity related to the performance of precision grip. This method will be described in more detail in the methods section of this thesis.

The primary motor area (M1), bilateral sensory motor related areas including the ventral premotor area (PMV), dorsal premotor area (PMD), supplementary motor area (SMA), intraparietal sulcus, cingulate motor area (CMA) and the cerebellum are of importance for skillful manipulation when control of fine precision grip forces are needed. Activity in these areas seems to be modulated by the level of precision required by the task, indicated by an increase in activity when the task requires very precise levels of force control (Binkofski et al. 1999a; Binkofski et al. 1999b; Ehrsson et al. 2003; Ehrsson et al. 2000; Ehrsson et al. 2001; Ehrsson et al. 2002; Gallea et al. 2005; Kuhtz-Buschbeck et al. 2001; Kuhtz-Buschbeck et al. 2008*).*

Using fMRI, the specific contribution of each of the active areas in the brain during skillful precision gripping has been studied extensively. Areas in the cerebellum and intraparietal sulcus have been reported to be involved in the implementation and/or storage of internal models (Bursztyn et al. 2006; Ehrsson et al. 2002; Kawato 1999; Olivier et al. 2007). Furthermore, the cerebellum, together with SMA and cingulate areas, seem to be involved in adjustments of grip force (Bursztyn et al. 2006). The role of the cerebellum in force control is further highlighted by Nowak et al. who showed in a subject with cerebellar agenesis impaired ability to scale grasping force and to perform predictive adjustments of grasping during a transport task in comparison with healthy control subjects (Nowak et al. 2007). Dafotakis and colleagues (Dafotakis et al. 2008) used TMS (Transcranial magnetic stimulation) to stimulate left M1, PMV and anterior intraparietal sulcus (AIP) respectively during grasping and lifting of objects with unpredictable weight. The results showed that TMS over PMV interfered with the ability to predictably scale grip force, whereas stimulation over AIP resulted in decreased ability to perform reactive adjustments of grip force. Stimulation over M1 did not affect the ability to predict and scale grip force (Dafotakis et al. 2008).

A common feature of the studies described above is that the objects used for manipulation are mechanically stable. In two fMRI studies, Milner et al. (Milner et al. 2006; Milner et al. 2007) used tasks involving manipulation of mechanically unstable objects. The aim was to explore the neural mechanisms that contribute to the ability to manipulate objects with complex dynamics. The authors found that activity in the cerebellum appeared to discriminate features of the manipulation dynamics that were not discriminated in M1. Cerebellar activity differed depending on the complexity of the manipulated object giving further support for the theory that cerebellar activity in this type of task represents the implementation of feedback processes or an internal model used to stabilize the arm and control the fingers (Milner et al. 2006; Milner et al. 2007).

Given the results from previous research, it appears that different brain regions, although part of the same “grasping network”, are more or less activated depending on whether the task predominantly involves production of force magnitude or precise control of force direction. As previously mentioned the tasks that have been used to investigate the neural correlates of precision gripping have either involved stable objects for manipulation or used tasks in which the required level of absolute force production or finger coordination/precision could not be varied independently. In addition, some studies might have included precision grip tasks that were not challenging enough to activate areas specifically associated with dexterous manipulation, should such exist (Kuhtz-Buschbeck et al. 2008).

By using unstable objects for manipulation with different levels (high-low degree of challenge) of force constant and instability it is possible to investigate regions primarily associated with either generation of force or finger coordination during precision gripping, within one task, controlling for sensory motor processing common to all objects. The aim of the fMRI study included in this thesis was to map the brain regions predominantly involved in control of force magnitude or direction during manipulation of unstable objects, and this has not been extensively studied previously.

1.4 CERERAL PALSY

The motor system and aspects of hand function in typically developing individuals has been described in the preceding sections of this introduction. The sections below will describe some aspects of the motor system when development is disrupted by injury to the immature brain and how this affects hand function in one of the most common neuromotor disabilities in childhood, cerebral palsy (CP).

The following is a recently proposed definition of cerebral palsy: “Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, 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” (Rosenbaum et al. 2007).

The prevalence of cerebral palsy in live births in Sweden is 2.18-2.40/1000 (Himmelmann et al. 2010; Westbom et al. 2007). A motor impairment predominantly affecting one side of the body is seen in about 30-40% of children diagnosed with CP (Himmelmann et al. 2010; Westbom et al. 2007). This type of CP can be either arm or leg-dominated, and is classified as unilateral spastic CP according to the Surveillance of Cerebral Palsy in Europe definition (SCPE) (2000).

1.4.1 Lesion types and associations with motor function

Conventional magnetic resonance imaging (MRI) is a widely used imaging modality that can provide information on the pathophysiology as well as to some extent the timing of the underlying insult to the brain in CP (Bax et al. 2006; Keogh and Badawi 2006; Kwong et al. 2004) and will be described in more detail in the methods section of this thesis.

In the definition presented above it is stated that CP is “attributed to non-progressive disturbances that occurred in the developing fetal or infant brain” (Rosenbaum et al. 2007). Early theories suggested that single factors, such as intrapartum asphyxia, as a single and primary cause of CP. However, it is now well established that a multitude of factors, often in combination, can cause or increase the risk of disturbances to the developing brain resulting in a clinical diagnosis of CP. Example of such factors are, genetic polymorphisms, multiple pregnancy, pre-term birth, intra uterine infections, inflammation, hypoxia and ischemia (Bax et al. 2006; Keogh and Badawi 2006).
Different structures of the brain are more vulnerable to injury during certain periods of development. Early insults, occurring during the first and second trimester of

pregnancy, often cause maldevelopments, while white matter structures, and in particular the periventricular white matter, is more susceptible to injury later on in pregnancy (in the late second to early third trimester). This in contrast to cortical and subcortical (e.g. thalamus and basal ganglia) grey matter structures that are more vulnerable around the time of birth (Accardo et al. 2004; Krageloh-Mann and Horber 2007). Brain maldevelopments have been reported as the underlying pathology causing unilateral spastic CP in about 10-16% of the cases, periventricular white matter lesions account for 34-36%, and cortical or deep grey matter lesions, mainly middle cerebral artery infarcts, account for 27-31% (Bax et al. 2006; Krageloh-Mann and Cans 2009).

The relationship between overall motor function in CP and lesion characteristics as delineated by visual inspection of conventional structural MRI is to some extent understood. Periventricular white matter lesions, with mild white matter loss are often associated with a mild degree of overall motor impairment, whereas extensive white matter loss leads to more severely impaired function (Melhem et al. 2000; Serdaroglu et al. 2004; Staudt et al. 2000). Lesions that affect grey matter (cortex, thalamus or basal ganglia) have been reported to cause moderate to severe motor impairments (Krageloh-Mann et al. 2002; Wiklund and Uvebrant 1991).

The studies in which aspects of hand function in children with unilateral CP have been investigated specifically in relation to lesion characteristics also indicate that the extent of the lesion (Forssberg et al. 1999; Staudt et al. 2000) and degree of dysgenisis in the corticospinal tract, for example, described by a symmetry index calculated from the absolute area of the cerebral peduncles as measured on MRI (Duque et al. 2003) is related to the severity of hand motor impairment.

It is possible for individuals who present with the clinical symptoms of cerebral palsy to have normal MRI on visual inspection (Bax et al. 2006; Krageloh-Mann and Cans 2009). It is likely that visual inspection of MR images is not sensitive enough to detect sublte abnormalities, that, indeed, are present. For example Son et al., who reported focal lesions to the corticospinal tract detected by diffusion tensor imaging (DTI) in patients with unilateral cerebral palsy who had no focal lesion on visual inspection of conventional structural MRI (Son et al. 2007). This indicates, that this imaging tool increases sensitivity of detecting structural brain abnormalities in this group of patients.

Diffusion tensor imaging is a non-invasive imaging technique that allows for in vivo assessments of tissue microstructure (Beaulieu 2002) and will be described in more detail in the methods section of this thesis. Over the recent years, some studies have been published that have focused on the relationship between diffusion measures in

the motor tracts and overall severity of CP, categorised into “mild”, “moderate”, “severe” (Glenn et al. 2007), or as measured by the Gross Motor Function Classification System (GMFCS) (Trivedi et al. 2010; Yoshida et al. 2010). There are very few studies published that have specifically focused on associations between diffusion MRI and hand function in CP (Bleyenheuft et al. 2007; Glenn et al. 2007). Findings from these studies indicate that diffusion MRI correlates with different aspects of hand function. Only one of these studies has focused on unilateral CP and quantitative analyses of diffusion MRI , and the results show that a symmetry index between the area of the left and right cerebral peduncle as defined on color coded DTI maps correlated more strongly with clinical assessments of hand function than did measurements of damage to the cortico-spinal tract as described by a symmetry index between the area of the left and right cerebral peduncle on conventional structural MRI (Bleyenheuft et al. 2007).

1.4.2 Re-organization of the motor system in unilateral CP

An early injury to the developing brain can result in re-organization of the motor system. Transcranial magnetic stimulation (TMS) has been used by several research groups to study plasticity in the cortico-motor system in children with unilateral CP (Carr 1996; Duque et al. 2003; Eyre et al. 2007; Guzzetta et al. 2007b; Staudt et al. 2002; Thickbroom et al. 2001; Vandermeeren et al. 2003). Carr and co-workers, were among the first to show that descending projections from the motor cortices can be re-organized in children with unilateral CP (Carr 1996).

Projections to the hemiplegic hand can be contralateral (which is the typical pattern), ipsilateral, or mixed (i.e. the hemiplegic hand receives projections from both hemispheres) (Carr 1996; Guzzetta et al. 2007b; Staudt et al. 2004; Thickbroom et al. 2001). Re-organization of motor projections has been found with all lesion types (white matter lesions, cortical-subcortical lesions and malformations) (Guzzetta et al. 2007a; Staudt et al. 2004). It has been suggested that the presence of fast conducting ipsilateral projections is associated with poor functional motor outcome (Carr 1996; Eyre et al. 2007; Vandermeeren et al. 2003). This type of re-organization of descending pathways seems to be unique to the motor system since sensory projections have not been reported to re-organize in the same manner (Guzzetta et al. 2007b). This indicates that a hemispheric dissociation between sensory input and motor output can occur, which may be a contributing factor to the poorer functional outcome seen in subjects with ipsilateral projections (Guzzetta et al. 2007a; Staudt et al. 2006; Thickbroom et al. 2001).

The mechanisms behind the re-organization in the descending motor pathways following an early insult to the brain have been described in previous studies. Fast conducting ipsilateral motor pathways are, as earlier described in this introduction, part of normal development. These pathways are dependent on neural activity in the cortical motor areas and will be weakened during development, while the contralateral pathways are strengthened, and most ipsilateral projections will eventually withdraw if not activated (Eyre 2007; Martin 2005). Early lesions are related to a more favorable outcome, indicating that the timing of the insult to the brain can be of great importance for the efficacy of these persisting pathways (Staudt et al. 2004).

Eyre and colleagues (Eyre 2007; Eyre et al. 2007) have presented evidence that suggests that this type of re-organization should be considered to be a result of activity-dependent, competitive withdrawal of contralateral projections from the affected cortex, rather than a reparative compensatory mechanism (Eyre 2007; Eyre et al. 2007). There have been no reports of normal hand function in children with unilateral CP and ipsilateral motor projections from the un-affected hemisphere, see Staudt 2010 for review (Staudt 2010), which indicates that re-organization cannot fully compensate for the early damage to the motor system.

It has been reported that individuals with unilateral CP and ipsilateral motor projections also can have re-organized cortical motor activation patterns when investigated with fMRI during passive and active hand movements (Staudt et al. 2006; Staudt et al. 2002; Thickbroom et al. 2001). Moreover, this pattern of cortical activation does not necessarily follow the motor projection pattern indicated by TMS (Staudt et al. 2002; Thickbroom et al. 2001).

1.4.3 Hand function in unilateral cerebral palsy

Hand function is always affected in unilateral CP and the impairment can vary from just slight clumsiness to difficulties in performing voluntary movements. The impairment often involves increase in muscle tone, deformities of the joints, slowness of movements, muscle weakness and poor coordination (Arner et al. 2008; Uvebrant 1988), impaired sensibility (Krumlinde-Sundholm and Eliasson 2002) and presence of mirror movements (Kuhtz-Buschbeck et al. 2000). Children with unilateral CP often have impaired grip-lift synergy (Forssberg et al. 1999) and also show impairments in the scaling of grip forces, by using excessive amounts of force (Eliasson et al. 1995b; Mackenzie et al. 2009), as well as poor coordination when releasing objects during grasping (Eliasson and Gordon 2000; Gordon et al. 2003).

The few studies that describe development of hand function in individuals with unilateral CP show that differences in individual patterns of development can be expected due to the great inter-individual differences in severity of the impairment (Hanna et al. 2003; Holmefur et al. 2010) and, in addition, that development occurs over a longer period of time than what is expected in typically developing children (Eliasson et al. 2006a).

Although it is not within the scope of this thesis it is important to point out that an individual's ability to use his or her hands in different activities is highly influenced by any accompanying disturbance (such as sensory impairments, impairment of perception, cognition, presence of secondary musculoskeletal problems and/or epilepsy) in addition to lesion characteristics and organization of motor projection patterns.

Since children with unilateral CP have one hand that is more impaired a common strategy in many everyday activities is to rely solely on the "good" hand.
Many activities require coordinated use of both hands (e.g., opening a can of soda or pulling up a zipper) and poor bimanual performance is a common impairment in children with unilateral CP (Steenbergen et al. 2008). A number of assessment tools designed to measure performance of bimanual activities have been developed during recent years. The Assisting Hand Assessment (AHA) (Krumlinde-Sundholm et al. 2007) is the only test of bimanual performance that has evidence for reliability and validity for its intended purpose (Greaves et al. 2010). There are also a number of norm referenced timed tests of gross manual dexterity available, such as the Box and Blocks test (Mathiowetz et al. 1985), and this is the assessment, together with the AHA, that is used in three of the studies in this thesis and will be described in more detail in the methods section.

As outlined above, many children with unilateral CP also have impaired ability to scale their grasping force and control the direction of the forces produced and these are also abilities of great importance for performance of fine motor skills. Interestingly, there is to date, no available clinical assessment tool that can capture the ability to control the direction and magnitude of fingertip forces during grasping in children. To accurately assess an individual's ability to control fingertip forces during manipulation is likely to be clinically useful for evaluation of treatment outcome.

Test development is the process of producing a measure of some aspects of an individual's knowledge, skill, ability, interest, attitudes or other characteristics by developing items and combining them to form a test, according to a specified plan (American Educational Research Association 1999). During this process the purpose and contents of the test needs to be considered together with the format and context

in which the test will be used. In addition, test procedures such as administration and scoring needs to be determined (American Educational Research Association 1999). At the core of test development lays the concept of validity. Validity can be defined as; the degree to which evidence and theory support the interpretations of test scores entailed by proposed uses of the test (American Educational Research Association 1999). The internal scale validity is based on the internal structure of a test. This type of validity evidence indicates to what extent the relationships among test items match the defined construct of the test (Goodwin 2002a).

The first study of this thesis aims at assessing evidence of internal scale validity for a recently developed test, which was designed to measure the ability to control force magnitude and force direction, when applied in a population of typically developing children.

2 AIMS OF THE THESIS

The overall aim of this thesis is to further expand our knowledge of the neural correlates of precision grip during manipulation of unstable objects and to describe how damage to the motor system affects hand function in children with unilateral CP. The specific aims of the four studies are outlined below:

Study I

The aim of this study was first; to analyze the internal scale validity of the Strength–Dexterity Test in a typical pediatric population, and second, to investigate how the Strength–Dexterity Test relates to tests of pinch strength and manual dexterity. Third, to examine how performance varies with age and whether there are any sex differences.

Study II

The aim of this study was to study the neuroanatomical correlates of fingertip force vector direction and magnitude control using functional magnetic resonance imaging.

Study III

The aim of this study was to investigate associations between hand function, brain lesion characteristics, and motor projection patterns in children with unilateral CP using transcranial magnetic stimulation.

Study IV

The aim of this study was first, to assess microstructure of corticofugal fibers, and second, to explore associations between tract injury as assessed by quantitative analysis of diffusion magnetic resonance imaging and hand function in children with unilateral CP.

3 METHODS

A number of different methods were used in the studies included in this thesis. The different methods include neuroimaging and neurophysiological techniques in addition to assessments measuring different aspects of hand function. In the sections below a brief study outline (Table 1) will be given, followed by details on the participants, recruitment process and procedure during data collection together with descriptions of assessments, methods (Table 4) and statistical analyses (Table 5) used in the four studies.

3.1 STUDY OUTLINES & DESIGN

A cross-sectional design was used to examine the internal scale validity of the SD-test (Study I) and to further develop the test to suit a pediatric population. Hand function data were collected on 56 typically developing children over the ages 4-17 years. Pilot data were also collected on 6 children with bilateral CP (ages 10-17 years), with hand motor impairment of varying degree (unpublished data). Data on the children with CP were collected to explore whether the SD-test has the potential to discriminate finger tip force co-ordination in persons with CP.

In Study II, fMRI was used to measure brain activity associated with compression of four hand held metal springs (for illustration of spring, see page 23) with different mechanical properties, representing an experimental 2×2 factorial design with two levels of force requirement and instability, respectively. A convenience sample of 19 right-handed healthy males was recruited to participate in the study.

The data for Study III and IV were collected from a convenience sample of 17 children with unilateral CP. Study III includes 17 and Study IV includes 15 children. Two of the 17 children included in Study III were excluded from Study IV due to poor quality of the diffusion tensor imaging data. Study IV also included a group of age and sex matched typically developing children (n=24) for MRI.

Table 1. Summary of study aims, design, number of participants and methods included in the four studies

Study	Aim	Design	Participants	Methods
I	To assess the internal scale validity of the SD-test in a typically developing pediatric population	Cross-sectional study	Typically developing children, n=56 Children with bilateral CP, n=6 Total n=62	SD-test, B&B test, Measurement of pinch strength
II	To describe the neural correlates of fingertip force vector direction and magnitude control	Experimental cross-sectional study with a 2X2 factorial design	Adult males, n=19	Items from the SD-test and fMRI
III	To investigate associations between hand function, brain lesion characteristics, and motor projection patterns in children with unilateral CP	Cross-sectional study	Children with unilateral CP, n=17	The AHA, B&B test, TMS, conventional structural MRI
IV	To assess microstructure of corticofugal fibers and to explore associations between tract injury hand function in children with unilateral CP	Cross-sectional study	Children with unilateral CP, n=15 Typically developing children, n=24 Total n=39	B&B test, conventional structural MRI and diffusion MRI

3.2 PARTICIPANTS, RECRUITMENT PROCESS AND DATA COLLECTION

3.2.1 Participants: Study I

In Study I a sample of 56 typically developing children (30 males, 26 females; aged 4 years 10 months to 17 years 3 months) were recruited from local nurseries and schools in the Stockholm area. Children who had a history of neurological or neurodevelopmental problems were excluded and participants were divided into four age categories (see Table 2). Individual characteristics of the six children with bilateral CP included in the study are described in Table 3, with regards to sex, age, manual ability and gross manual dexterity.

Table 2. Number of typically developing children in each age category, Study II**,** m=males, f=females.

Age category	1 (59- 83 months)	2 (84-119 months)	3 (120-155 months)	4 (156-208 months)
n	21 (m=12/f=9)	15 (m=7/f=8)	10 (m=4/f=6)	10 (m=6/f=4)

Table 3. Description of the children with CP with regards to gender, age, manual ability (MACS), gross manual dexterity (Box and Blocks Test, B&B) included in Study II (unpublished data).

Subject	Age category	MACS	B&B dominant hand	B&B non-dominant hand
1. Female	4 (156-208 months)	II	51	27
2. Male	3 (120-155 months)	II	45	32
3. Male	4 (156-208 months)	II	22	18
4. Female	4 (156-208 months)	II	30	24
5. Male	3 (120-155 months)	IV	19	16
6. Male	3 (120-155 months)	II	28	28

3.2.2 Data collection: Study I

The data collection took place either at nursery, school or at home. First, a standardized clinical test (Box and Blocks test) was administered followed by an assessment of maximal pinch strength. The SD-test was always administered last. Instructions and demonstration of the correct finger posture were given (see Figure 2, page 23 in the methods section), and the participants got the opportunity to familiarize themselves with the task. Breaks were provided when needed to prevent fatigue and maintain concentration. On average, the test procedure for each participant lasted approximately 15 minutes. The procedure for data collection did not differ between typically developing children and children with CP.

3.2.3 Participants: Study II

In Study II a convenience sample of 19 right-handed healthy males were recruited to participate in the study. Exclusion criteria were a history of neurological problems. Imaging data from one participant were excluded because of a technical failure with the MR-scanner, and data from another two participants who failed to perform according to instructions were also discarded. Sixteen participants (age: 26-42, M=32 ± 4 years) were included in the final analysis.

3.2.4 Data collection: Study II

All experiments were conducted at the MR-center of the Karolinska University Hospital in Stockholm, Sweden. All participants filled out forms concerning MR-safety procedures. The experimental paradigm was described to the participants and they were given time to try out the different springs while they were instructed on how to position their hand and fingers during the experiment in the scanner.

Each participant performed two scanning sessions. Each trial of the experiment consisted of two parts – Instruction and Condition. During the scanning sessions, an experimenter would stand next to the participant and exchange springs according to a pre-specified task order, identical for all participants. The order was constructed using permutations of the five conditions; HF/LI (high force/low instability), LF/LI (low force/low instability), HF/HI (high force/high instability), LF/HI (low force/high instability), and rest. An E-prime script (Psychological Software Tools, Inc.) was used to present the verbal instructions and metronome to the participants and also give instructions to the experimenter on the next spring to be presented and a countdown until the next stimulus presentation or rest. Two different instructions were given to participants, corresponding to either the rest or active conditions: “Rest”; “You will now be given a new spring. Compress the spring in beat with the metronome.” The experimenter responsible for exchanging the springs also monitored the participant’s behavior and logged any performance errors. All participants included in the final analysis completed all conditions successfully.

3.2.5 Participants: Study III and IV

Study III and IV consist of data from the same data collection. The children with unilateral CP were recruited from a convenience sample, with the aim of including children with a wide range of hand function. Inclusion criterion was a diagnosis of unilateral CP according to Surveillance of Cerebral Palsy in Europe criteria (2000). Exclusion criteria were epilepsy, hearing impairment, and ventriculo-peritoneal shunt. Study III included 17 children with unilateral CP (9 males, 8 females; mean age 11.4, range 7–16 years), and Study IV included 15 children (6 male, eight females, mean age 12.4, range 7-16 years). In Study IV, two children from the original group were excluded due to poor quality of diffusion imaging data.

In Study IV, a convenience sample of 24 children with no history of neurological or neurodevelopmental problems (9 male, 15 female; mean age 12.7 years, range 8-17 years) were included as controls for comparisons in diffusion measures between children with unilateral CP and typically developing children.

3.2.6 Data collection: Study III and IV

Since the rather extensive data collection in Study III and IV could be quite tiring for the younger children, data were in some cases collected at two occasions and the order of the different examinations and assessments was individual to meet the needs of each individual child. Data were collected at two different locations at the Karolinska University Hospital; the MR-Center and the department of

Neurophysiology. The children were first assessed by pediatric neurologist. This was done to confirm the clinical diagnosis of unilateral CP.

After this the assessments of hand function were conducted. Children and their parents filled in questionnaires concerning MR and TMS-safety prior to all MRI and TMS experiments. The children got the opportunity to familiarize themselves with the environment in the scanner room before going into the scanner and one experimenter was inside the scanner room during all scanning. A break was provided between the MRI and TMS examination. All children got the opportunity to listen to music or a story during the MRI, and watch a movie of their choice during the TMS experiment. All in all, the total time each participant had to spend at the hospital was around 4h (including break).

The children who were recruited as controls were scanned using the same MRI protocol and procedure for the scanning as the children with unilateral CP. The total time the controls had to spend at the hospital was around 1.5h.

3.3 MATERIALS & ASSESSMENTS

All methods, materials and classifications used in this thesis will be presented in detail in the following section, and are summarized in Table 4. The sections on neuroimaging and neurophysiology will begin with a brief introduction before the specific protocol for each study is presented.

Table 4. Summary of the different classifications, assessments of hand function, neuroimaging and neurophysiology methods used in the four studies.

Materials/Methods	Study I	Study II	Study III	Study IV
MACS			X	X
GMFCS			X	X
AHA			X	
B&B test	X		X	X
SD-test	X	X		
Pinch meter	X			
Assessment of mirror movements			X	
Assessment of 2-point discrimination			X	
Conventional structural MRI		X	X	X
Diffusion tensor imaging				X
fMRI		X		
TMS			X	

3.3.1 Manual Ability Classification System (Study III-IV)

The Manual Ability Classification System (MACS) was used to describe how the children with unilateral CP included in Study III and IV used their hands to handle objects in daily activities. The MACS describes five levels (I-V). Children in level I can handle objects easily and successfully, while children in level V do not handle objects and have severely limited ability to perform even simple actions (Eliasson et al. 2006b).

3.3.2 Gross Motor Function Classification System (Study III-IV)

The Gross Motor Function Classification System (GMFCS) was used to describe gross motor function in the children with unilateral CP included in Study III and IV. Children in level I can walk indoors and outdoors, and climb stairs without limitations. Children in level V have physical impairments that restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures and all areas of motor function are limited (Palisano et al. 1997).

The MACS and the GMFCS were only used to describe manual ability and gross motor function in the studied population of children with unilateral CP and the data obtained are therefore not part of statistical analyses.

3.3.3 Assisting Hand Assessment (Study III)

The Assisting Hand Assessment (AHA) was designed to measure how effectively the hemiplegic hand can handle different objects in bimanual activities. The test is a videotaped play or board-game session for children aged 18 months to 12 years; for children over 12 years of age, a research version of the test was used. The AHA is scored from the video with 22 items rated on a 4-point scale. The raw score is converted to a scaled score (0–100%) (Krumlinde-Sundholm et al. 2007).

3.3.4 Box and Blocks test (Study I, III, IV)

The Box and Blocks test (B&B test) is a norm referenced timed test of gross manual dexterity in which each hand is assessed separately. This task requires the participant to move as many blocks as possible within 60 seconds from one side of a box to the other, passing a 20cm high partition (Mathiowetz et al. 1985).

3.3.5 Strength-Dexterity test (Study I-II)

The Strength-Dexterity test (SD-test) (Valero-Cuevas et al. 2003) consists of compressing a variety of springs to their solid length (i.e. the coils touching) without buckling. The springs are characterized by two indices: the strength index (which

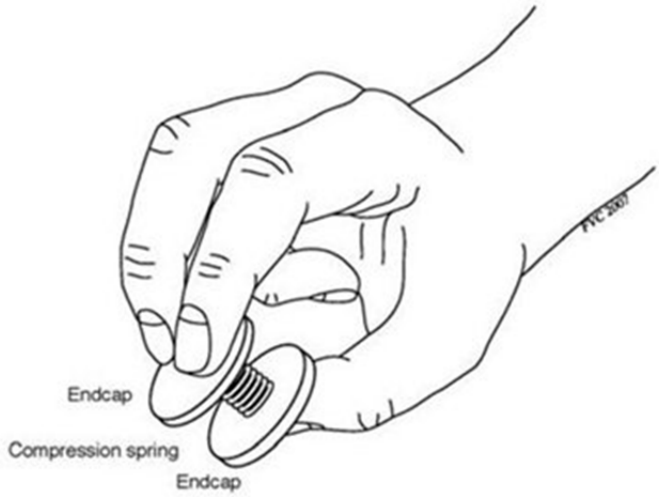


Figure 2. Compression spring and correct finger position.

specifies the force required to compress the spring and is indicated by spring specification labeled 1–13) and the dexterity index (which specifies the degree of mechanical instability, i.e. the tendency of the spring to buckle, and is indicated by spring specification labeled A–H). Both indices are a function of the geometry of the spring and physical properties of the material used, and are adjusted independently for the different springs (see Figure 1). We used a subset of the original Strength–Dexterity Test kit, in Study II, which consists of 82 compression springs. Only springs that had strength requirements below and slightly exceeding each participant's individual maximal pinch force were used. This meant that an individual sub-set of springs were used for each participant. Springs were presented in random order and a binary score was used to record successful performance (1) or failure (0).

3.3.6 Pinch meter (Study I)

Maximal strength for opposition pinch (using both the index and middle fingers) was measured with a pinch meter (model PG-60 pinch gauge; B&L Engineering, Tustin, CA, USA).

3.3.7 Assessment of mirror movements (Study III)

Mirror movements were assessed with three repetitive tasks: opening and closing of the fist, opposition of index finger and thumb, and sequential finger opposition (Woods and Teuber 1978). These tasks are performed with one hand while the non-active hand is observed to detect possible mirror movements. Mirror movements were categorized as follows: 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.

3.3.8 Assessment of two point discrimination (Study III)

Aspects of sensory function were assessed using the 2-point discrimination test (tested on the fingertips of digits II–IV). Function was considered normal when discrimination of at least 3mm was possible, decreased when 5mm of spacing was discriminated and poor when the child was not able to discriminate at 5 to 7mm spacing (Krumlinde-Sundholm and Eliasson 2002).

3.4 NEUROIMAGING

All neuroimaging experiments were conducted at the MR-center of the Karolinska University Hospital in Stockholm, Sweden. Images were acquired on a 1.5 Tesla MRI system (Signa Excite, GE Medical Systems, Milwaukee, WI, USA).

3.4.1 Introduction: Conventional structural MRI

Conventional MRI is based on the detection of the signal from the hydrogen nuclei ^{1}H (i.e. protons) in water (H_2O). MRI uses the phenomenon of nuclear magnetic resonance to image body tissue. When a person's head is placed in the MR scanner the magnetic spin of the protons in the brain tissue align with the scanner's magnetic field. To acquire an image a radio frequency (RF) pulse is applied, which excites the protons and makes them absorb energy and deviate (flip) from their original positions. After the RF-pulse, the protons will slowly recover and return to their original states in re-alignment with the field. A receiver coil surrounding the head in the scanner detects the faint signal echo from the protons and this signal is ultimately transformed into an MRI image. The recovery process is a so-called relaxation process. The relaxation time is the time it takes for the protons to recover and depends on their chemical environment. The contrast in MRI is due to the difference in relaxation properties of protons in different chemical environment (i.e. tissues) and is reflected in the detected signal. Depending on when during the relaxation period the signal is measured different types of tissue will become more visible. The echo time (TE, i.e. the time between excitation and when the signal is measured) and the repetition time (TR, i.e. time between two RF-pulses) are timing parameters and by varying these, contrast between different tissue types and/or pathological changes are obtained in the images (Jezzard 2001; McRobbie 2007).

T_1-weighted images have short TR and TE, and are known as "anatomy scans", since the boundaries between different tissue types appears very clear in this contrast. Mature white matter appears bright, grey matter grey and cerebrospinal fluid dark in this sequence (Jezzard 2001; McRobbie 2007).

T_2-weighted images, on the other hand can be referred to as "pathology scans", since abnormal collections of fluid appears bright in this contrast and mature white matter is dark. A third sequence that is commonly used for lesion assessment is the FLAIR (Fluid Attenuated Inversion Recovery). This is also a T_2-weighted sequence in which a pre-pulse is applied to null the signal from cerebralspinal fluid so that pathology located close to the ventricles (such as gliosis) can be evaluated (Jezzard 2001; McRobbie 2007).

The imaging protocol used (Study III and IV) to visually assess the lesions in the children with unilateral CP included T_1-weighted, T_2-weighted and a FLAIR sequence and will be described in detail in the section below.

3.4.2 Structural MRI acquisition (Study II, III and IV)

The protocol included the following sequences: Axial and coronal T2-weighted and coronal FLAIR images (in plane resolution 0.43mm², 4mm slice thickness with 1mm spacing for axial, and no spacing on coronal images), and a 3D high resolution T1-weighted image (voxel size 0.86 x 1 x 0.86mm³).

3.4.3 Introduction: Diffusion MRI

Diffusion-weighted MRI (DWI) is a non-invasive technique that allows for in-vivo assessments of tissue microstructure and the contrast mechanism is rather different from that of conventional structural MRI. The contrast is based on the movement of water molecules in the tissue and a number of factors, in addition to the random thermal motion (Brownian motion), influence this. The physical location and displacement of the molecules are encoded through the application of a diffusion-sensitizing gradient pulse. After a delay (typically of 20-50msec) a second diffusion-sensitizing gradient pulse is applied through which the displacements of the molecules are measured. The distance the molecules can move in space might not be the same in all directions. When the molecules can move freely and are not hindered by barriers in the tissue diffusion is isotropic, i.e. the same in all directions (As reviewed in (Beaulieu 2002; Mori and Zhang 2006; Roberts and Schwartz 2007)). When there are oriented barriers in the tissue, like in myelinated white matter, diffusion becomes anisotropic which means that the molecules move more freely in one direction along the fibers (Basser and Pierpaoli 1996).

Diffusion measurements must be made in at least six different directions and can only be measured in one direction at the time which means that several images need to be acquired. The information obtained from each voxel can then be used to calculate a tensor, a 3x3 matrix that has magnitude and direction in 3-D space. The tensor is symmetric and can be decomposed into its three eigenvectors and eigenvalues ($\lambda_{1\text{-}3}$) which describe the three-dimensional diffusion properties in each voxel (As reviewed in (Beaulieu 2002; Mori and Zhang 2006; Roberts and Schwartz 2007))(Figure 3).

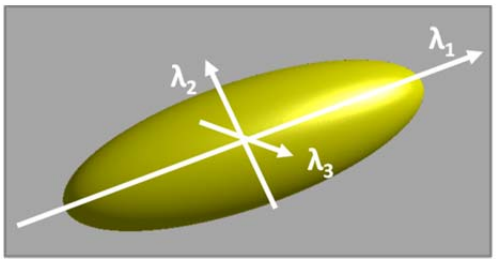


Figure 3. The diffusion tensor model.

The largest eigenvalue λ_1 represents diffusion along the principal axis which is assumed to be along the fibers and is referred to as "axial diffusivity". The smaller eigenvalues λ_2 and λ_3 represent diffusion perpendicular to the principal axis and the assumed orientation of the fibers. The mean of λ_2 and λ_3 is referred to as the "radial diffusivity". In Study IV of this thesis we used two different diffusion measures to describe the microstructure of the corticospinal tract, the mean diffusivity (MD) and the fractional anisotropy (FA). The MD is the mean of all eigenvalues $\lambda_{1\text{-}3}$ and reflects the isotropic average degree of diffusion and is thus not directionally dependent. This in contrast to the FA, that describes the degree of anisotropy (0= fully isotropic, 1= fully anisotropic) and is calculated by summary statistics based on the difference between λ_1, λ_2 and λ_3. The diffusion MRI protocol used in Study IV is described in detail in the section below.

3.4.4 Diffusion MRI acquisition (Study IV)

Diffusion weighted images were collected using a twice-refocused single shot EPI sequence (TR/TE=10000/76ms) with 6 b=0 images followed by DWI with 45 non-collinear gradient directions (Jones et al, 1999) and b=1000s/mm^2. Full brain coverage was achieved with isotropic voxels 2.3mm^3 (reconstructed to an in plane resolution of 1.72mm^2). The first b=0 image was discarded due to its higher baseline signal, leaving data sets that contained 5 b=0 images plus 45 gradient directions with b=1000s/mm^2.

Bilateral measurements of FA, MD, $D_{//}$ (axial diffusivity) and $D_{\perp}$ (radial diffusivity) were performed in two regions of interest (ROIs) along the corticofugal fibers by two independent observers, and two fiber tracts were generated with ROI1 and ROI2 as seed masks and waypoint masks respectively. A termination mask, which included the waypoint mask, was defined as all voxels inferior and superior to these masks. Both tracts were thresholded to retain 1% of the total number of generated fibers. The intersection of these tracts was calculated as the tract of interest, called the partial tract (Figure 4).

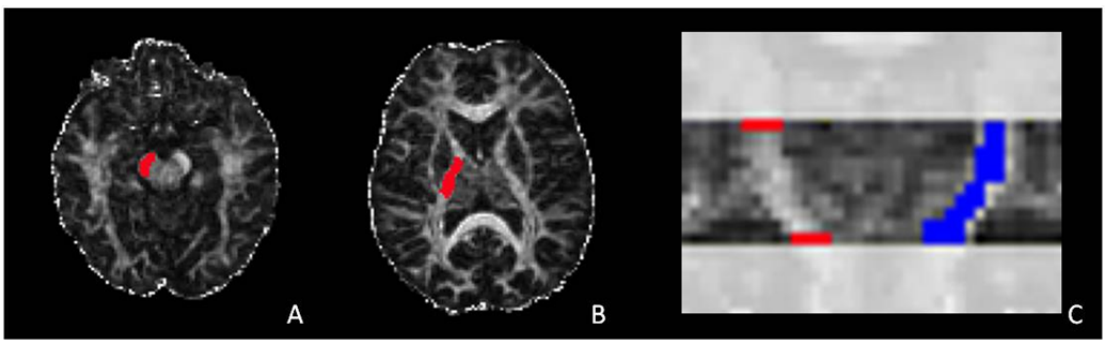


Figure 4. Illustration of regions of interest (ROIs, A-B) and the partial tract (C).

3.4.5 Introduction: Functional MRI

Functional magnetic resonance imaging (fMRI) is an indirect measure of neural activity that can be used in vivo. The contrast in fMRI is based on the close relationship between oxygen consumption and neural activity in the brain (Jezzard 2001). This is commonly referred to as the blood-oxygen-level-dependent (BOLD) contrast (Ogawa et al. 1992). Neural activity leads to local increases in blood flow. However, even though this increase is followed by an increased consumption of oxygen the increase does not match the oxygen delivery rate leading to a local decrease of deoxygenated blood and a change in the ratio between deoxygenated and oxygenated blood in the vessels in the area with increased neural activity. Oxygenated blood is not magnetic (diamagnetic) while deoxygenated blood is magnetic (paramagnetic), and this leads to changes in local distortions of the magnetic field applied. This effect of neural activity produces a small signal increase in that can be detected and measured during task performance (Jezzard 2001).

There are different design options for fMRI studies. We used a block design in the study included in this thesis (Study II) in which epochs of active conditions are compared to a rest condition/or baseline. The advantage with a block design during motor experiments is that it allows for many repetitions of each condition in alternated order which ensures that patient movement and changes in scanner sensitivity have similar impact on the signal changes acquired during each block of the experiment.

Following the image acquisition, which always includes a 3D volume, the fMRI data need to be prepared for statistical analysis in several different pre-processing steps. The first step of the pre-processing is to perform re-alignment. This means that the first image of the first session is used as reference and all subsequent slices are re-aligned to this image and a mean functional image is created. After this the functional and anatomical images are co-registered and in the next step segmented (this divides structural images into grey matter, white matter and cerebrospinal fluid). Following this the functional images are transformed into standard MNI (Montréal Neurological Institute) space, which makes it possible to compare results between subjects and studies, and last, smoothed to reduce the effects of random noise in the data. The parameters used during the processing of the data in Study III will be described in more detail below.

3.4.6 fMRI acquisition (Study II)

At the beginning of each scanning session, a high-resolution, three-dimensional spoiled gradient echo T1-weighted anatomical image volume of the whole brain (voxel size 1×1×1mm) was collected. Functional image data were then collected using a gradient-echo, echo-planar (EPI) T2*-weighted sequence with BOLD contrasts (Kwong et al. 1992; Ogawa et al. 1992), using the following parameters: TE = 40ms; field of view (FOV) = 22cm; matrix size = 64×64; flip angle = 90°; slice thickness = 5mm; slice spacing = 0.5mm; TR = 2.5s. Whole brain image volumes were constructed from 32 contiguous axial slices. At the beginning of the session, four ‘‘dummy’’ image volumes were scanned, but not saved, to allow for equilibration effects. A total of 600 functional image volumes were acquired from each participant.

3.5 NEUROPHYSIOLOGY

3.5.1 Introduction: Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) follows the principles of electromagnetic induction: an electric current in the stimulation coil produces a magnetic field, and a changing magnetic field induces a flow of electric current in nearby conductors - including human tissue (Wassermann 2008). It is a non-invasive technique that can be used to investigate function in central motor pathways (as reviewed by (Frye et al. 2008; Hallett 2007)) and can, for example, provide information on the underlying mechanisms of motor skill deficits in children (as reviewed by (Garvey and Gilbert 2004). When the motor cortex is stimulated this results in activity in a target muscle that can be measured via an EMG. In Study III, we used single pulse TMS which means that one stimulation was performed at a time and the elicited activity in the target muscle was measured after each stimulation. Motor evoked potentials (MEPs) can be defined as the electrical muscular response elicited by the stimulation during TMS. A number of different parameters of the MEP can be studied; the latency or central motor conduction time, the amplitude, the size, the stimulation thresholds, silent periods etc. (Wassermann 2008). The threshold of the MEP is commonly referred to as a measure of cortical excitability and usually presented as a percentage of stimulator output (Frye et al. 2008; Wassermann 2008).

In Study III of this thesis our primary aim was to investigate the cortico-motor projection pattern in children with unilateral CP. We used a “figure-of-eight” coil which allows for focal stimulation of a clearly definable and limited location. The “figure-of-eight” coil is essentially two round coils placed side by side, so that the magnetic field is focused in the junction point where the fields meet and is

maximum below the junction (as reviewed by (Frye et al. 2008; Hallett 2007). The protocol used is described in more detail in the following section.

3.5.2 TMS data acquisition (Study III)

A Magpro X-100 stimulator and a figure-of-eight coil (model C-B60, Medtronic Inc., Minneapolis, MN, USA) giving a peak magnetic strength of 2.5T at 100% stimulator output were used. Motor evoked potentials were recorded from one hand at a time via shallow-cupped silver/silver chloride surface electrodes (Nihon Kohden, Rosbach, Germany), placed bilaterally on the abductor pollicis brevis muscles. Our main aim was to determine the type of corticospinal organization. Because of this we adopted a protocol which gives reliable information about the type of projection pattern while reducing the total number of necessary pulses. Since children less than 10 years of age have higher motor thresholds than adults (Garvey and Mall 2008) we used a protocol in which we, if necessary, increased the stimulator output to a 100% to make sure we got reliable results. To reduce the number of necessary pulses we chose to calculate estimated motor threshold and a latency including both the central and peripheral motor conduction time. To find the optimal point that would elicit a reproducible MEP, the hand motor area of each hemisphere was stimulated progressively with 5% increments in stimulator output. An estimate of the motor threshold was determined as an indicator of the level of cortical excitability. The estimated motor threshold was defined as the lowest stimulator output that would elicit a reproducible MEP (amplitude ‡ 50 lV) in the relaxed target muscle in at least five out of 10 stimulations. The absence of ipsilateral MEPs was confirmed through an increase in the stimulator output to 100% while the scalp was searched in a 2cm radius around a spot symmetrical to the opposite side's optimal point.

3.6 STATISTICS

The statistical analysis methods and tools used in each study will be presented in detail in the sections below, and a summary is presented in Table 5.

Table 5. Summary of statistical methods and analyses tools used in the individual studies.

Methods and tools for statistic analysis	Study I	Study II	Study III	Study IV
Descriptive statistics	X	X	X	X
Spearman's rank correlation test			X	
Partial correlation analysis				X
Mann-Whitney U test				X
The Sign test				X
Rasch analysis	X			
Regression analysis	X			X
One-way analysis of variance (ANOVA)	X			
Analysis of functional imaging data in SPM5		X		
Analysis of diffusion tensor imaging data in FSL				X

3.6.1 Brief introduction to Rasch analysis (Study I)

The application of Rasch analysis in health outcome measures has markedly increased over recent years (Belvedere and de Morton 2010). A central assumption of the Rasch model is that the probability of a particular participant passing a particular test item is determined by two parameters: the ability level of the participant and the difficulty level of the item (Bond 2001). Both parameters are measures on the same interval scale, which represents the latent trait the test of interest is assumed to measure.

In a Rasch analysis raw scores are transformed into interval measures by a log odds transformation of the probability of a correct response, using the unit logits for calibrating items and measuring individuals. Test items are then listed in an ordered way and participants are ordered according to their abilities with respect to the measured trait. A higher measure indicates a more difficult item or better ability. The difficulty of each item is shown by the item calibrations; the higher the measure, the more difficult the item. Goodness-of-fit statistics are used to evaluate the degree of fit between the actual patterns of responses and the Rasch assumptions.
A test is by convention considered to have acceptable unidimensionality when at least 95% of the items fit the Rasch measurement model (Bond 2001; Wright 1994).

3.6.2 Study I: Data analysis and statistics

We applied a Rasch model analysis for dichotomous data (using WINSTEPS 3.65.0 software; www.winsteps.com) to examine whether the test items (i.e. the different springs) measured one single latent trait. An analysis was performed on the full set of raw data to examine internal scale validity and reliability of the SD-test. Reliability was evaluated in terms of whether the items could separate individuals into distinct levels of ability; the separation ratio was transformed into a strata index describing the number of significantly different levels of measures. Dimensionality was further examined by a principal components analysis of the standardized residuals. Regression analyses were then used to investigate whether the SD-test shared variance with pinch strength and performance on the B&B test, and to characterize developmental curves of performance on the three tests. Finally, sex differences in performance were analyzed using one-way analysis of variance. The level of statistical significance was set at $p<0.05$.

3.6.3 Study II: Data analysis and statistics

MRI data were processed and analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). All fMRI image volumes were realigned, co-registered to each individual's T1-weighted image (Ashburner and Friston 1997), segmented, normalized (Friston et al. 1995) using the template brain of the Montréal Neurological Institute (MNI) and spatially smoothed with an isotropic Gaussian filter to 8 mm full-width-at-half-maximum.

The fMRI data were modeled using a general linear model, where we defined four conditions of interest corresponding to the periods in each epoch when the participants compressed each of the four springs. Movement parameters (representing six degrees of freedom) were modeled as individual regressors in the design matrix. We used a ‘‘minimum statistic compared to the conjunction null’’ analysis (Nichols et al. 2005), corresponding to a logical AND operation between the active conditions. The significance of effects was assessed using t-statistics from every voxel in the brain to create statistical parametric maps, which were subsequently transformed into Z-statistics. Analyses were first performed for contrasts of interest within participants. A second-level random effects analysis, based on summary statistics of the data from each participant, was then performed to allow inferences at group level. We report activations that were significant at $p=0.01$ after correction for multiple comparisons using a False Discovery Rate (FDR) analysis (Genovese et al. 2002), meaning that on average less than 1% of the suprathreshold voxels are false positives. An extent threshold exceeding five active voxels was used for all contrasts. Significant local peak activations were labeled according to the results of the meta-

analysis made by Mayka et al., of the bounderies of the motor and premotor cortices as defined by fMRI (Mayka et al. 2006) and the SPM anatomy tool box (Eickhoff et al. 2005).

3.6.4 Study III: Data analysis and statistics

MRI Images were visually assessed for lesion type, location, and extent. Findings were grouped according to the primary pattern of damage as follows: white matter damage of immaturity (WMDI), focal infarct, or maldevelopment. Periventricular white matter reduction in WMDI was classified as mild or moderate if on visual assessment, <50% of the periventricular white matter bulk was reduced, and as severe when more than 50% of the white-matter bulk was reduced. Images were assessed in a consensus group consisting of an experienced neuroradiologist, a radiologist, and two pediatric neurologists.

From the TMS data collected, in addition to determination of the projection pattern, the mean duration from cortical stimulation to target muscle registration was calculated from the first three reproducible MEPs at the estimated motor threshold. Descriptive statistics were used to present the data from the different assessments of hand function. In addition, the Spearman's rank correlation test was used for exploration of associations between the B&B test and the AHA. The level of statistical significance was set at $p<0.05$.

3.6.5 Study IV: Data analysis and statistics

MR diffusion data were processed and analyzed with FSL 4.1.2 (Smith et al. 2006). All diffusion volumes were distortion-corrected and aligned to the first b=0 image. Diffusion tensor estimations and parametric maps were calculated. These included MD, FA, the dominant eigenvalue λ_1 = "diffusivity along the principal axis" ($D_{//}$), the mean of non-dominant eigenvalues $(\lambda_2 + \lambda_3)/2$ = i.e. the mean diffusivity along the two minor axis ($D_{\perp}$), and the tensor eigenvectors. Following this, the distribution of intra-voxel fiber orientations was estimated for subsequent probabilistic fiber tracking using ProbTrackX in FSL.

For comparison of diffusion measures between the CP group and the control group the Mann-Whitney U test was used. Side differences in diffusion measurements within subjects were tested with the Sign Test. For analyses that examined correlations between FA and B&B scores partial correlations were calculated to

control for a possible age effect. Exploratory regression analyses were performed with the dependent variable “B&B test score” and the independent variables FA, lesion type, and severity of periventricular white matter reduction. We used two-tailed tests and $p<0.05$ as cut off for significance.

4 SUMMARY & BRIEF DISCUSSION OF FINDINGS

4.1 STUDY I

As stated in the introduction, to date there are no available clinical tests that measure the ability to scale and control the direction of grip forces even though this is a well known impairment in children with unilateral CP. The aim of Study I was to investigate the internal scale validity of the recently developed SD-test and to develop a version of the test suitable to be used in a pediatric population.

The internal scale validity was evaluated in a two step Rasch analysis. Four items were found to have no calibration value and were removed during the initial analysis. A second and final analysis included 78 items and showed that all items except two demonstrated good fit to the Rasch model indicating a valid unidimensional scale. The 78-items were well distributed along the full calibration range and were appropriately targeted for the sample of typically developing children and the test could separate individuals into different strata (Figure 5).

Further statistical analysis showed positive correlations between the B&B test, pinch strength and the SD-test. Unique contributions (i.e. squared semi-partial correlation coefficients) of pinch strength and the B&B test to SD-test variance were 16.9% and 12.1% respectively. Shared pinch strength and B&B test variance accounted for the largest fraction of SD-test variance. This indicates that the SD-test measures not only strength and gross manual dexterity, but also a construct unique to the SD-test that is likely to reflect the ability to coordinate fingertip forces. Performance improved with age on all three tests and no significant sex differences in mean scores were found on the SD-test.

4.1.1 Results from unpublished pilot data (children with CP)

Interestingly, when eight trials from the six participants (both hands were tested for two participants, in the other cases only the dominant hand) with CP were added and a new exploratory Rasch analysis was performed, only minor changes were seen on the item difficulty scale; it did not cause any new items to show poor infit and/or outfit statistics, and person separation and reliability values remained the same. The participants with impaired hand motor function could be found in a wide range on the person measure scale (see Figure 5), which suggests that the SD-test has the potential to discriminate finger tip force co-ordination also in persons with CP, and indicates that their ability measures were not age dependent.

In summary, the results show that the SD-test has internal scale validity when administered in a typically developing pediatric population and indicates that this could also be the case in children with CP (unpublished data). The 78-item SD-test measures a uniqe unidimensional latent trait that is likely to reflect individual differences in dynamic control of the fingertip force vectors that includes both strength and gross manual dexterity. The study also showed that the SD-test test has the potential to be developed into a promising tool for assessing dexterity in typically developing children as well as children with cerebral palsy and impaired hand function.

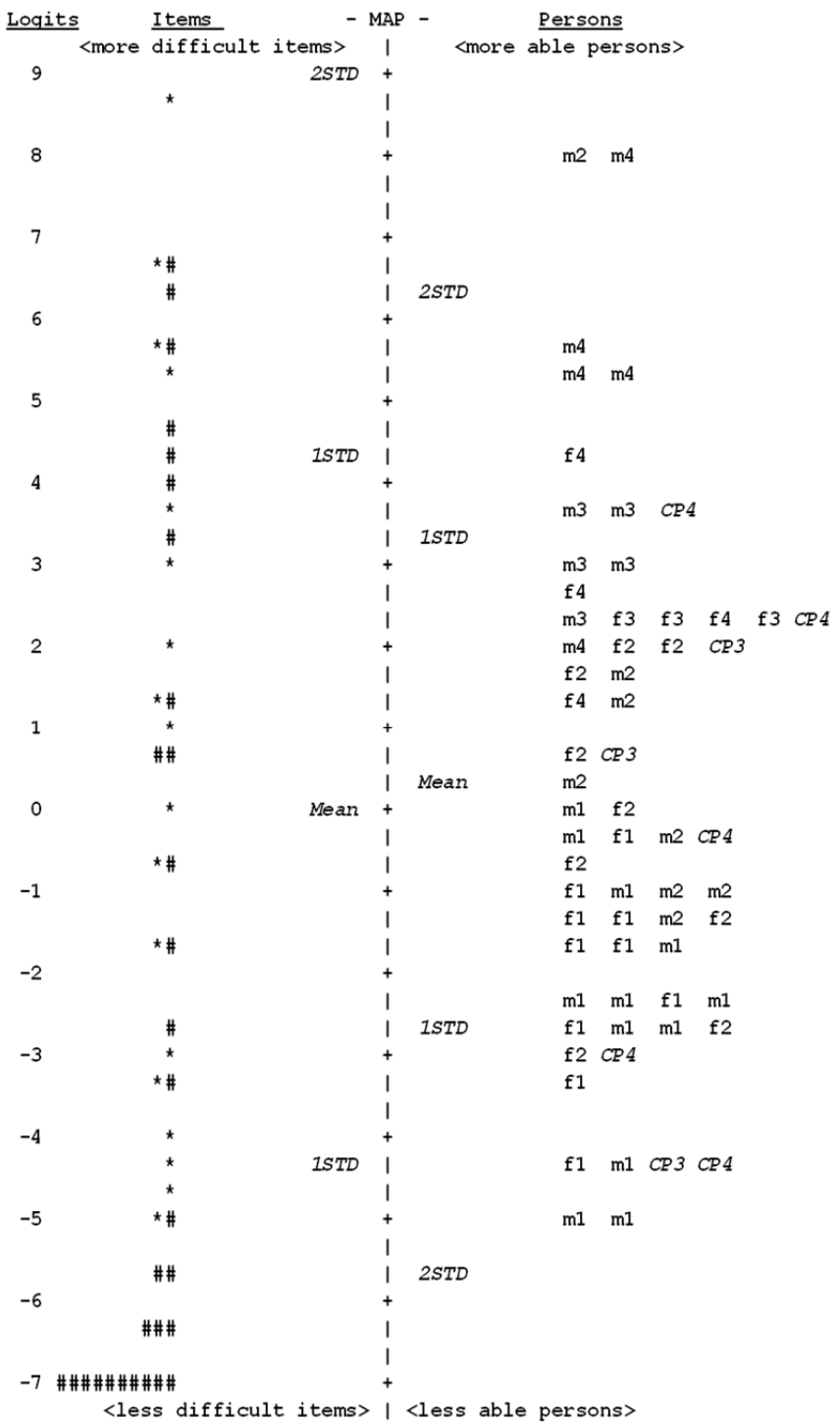


Figure 5. Map of item calibrations and person measures including 78 items and 56 typically developing children ⁄ adolescents. Each `#' represents two items and each `*' represents one item. Items at the higher end of the scale are more difficult than items at the lower end, and individuals at the higher end of the scale are more able than those at the lower end. The numbers indicate age categories). 2STD, marker indicating measures two standard deviations away from the mean measure; 1STD, marker indicating measures one standard deviation away from the mean measure, m = male; f= female, CP= individual with CP.

4.2 STUDY II

As outlined in the introduction, there are several studies that describe the neural network that is active during grasping of stable objects, and most of the tasks used in these studies involve objects that do not allow the required level of absolute force production or finger coordination/precision to be varied independently. The aim of Study II was to study the neuroanatomical correlates of fingertip force vector direction and magnitude control.

The dynamic control of fingertip force direction, represented by the main effect of high instability, was associated with activity in the bilateral precentral gyri, postcentral gyri/sulci at the level of the intraparietal sulci and bilaterally in the cerebellum (lobule VI), while fingertip force magnitude (i.e. the main effect of stiffer springs requiring higher forces) was related to unilateral activation of the (contralateral) precentral gyrus and bilateral cerebellum as well as activity in occipital and temporal regions.

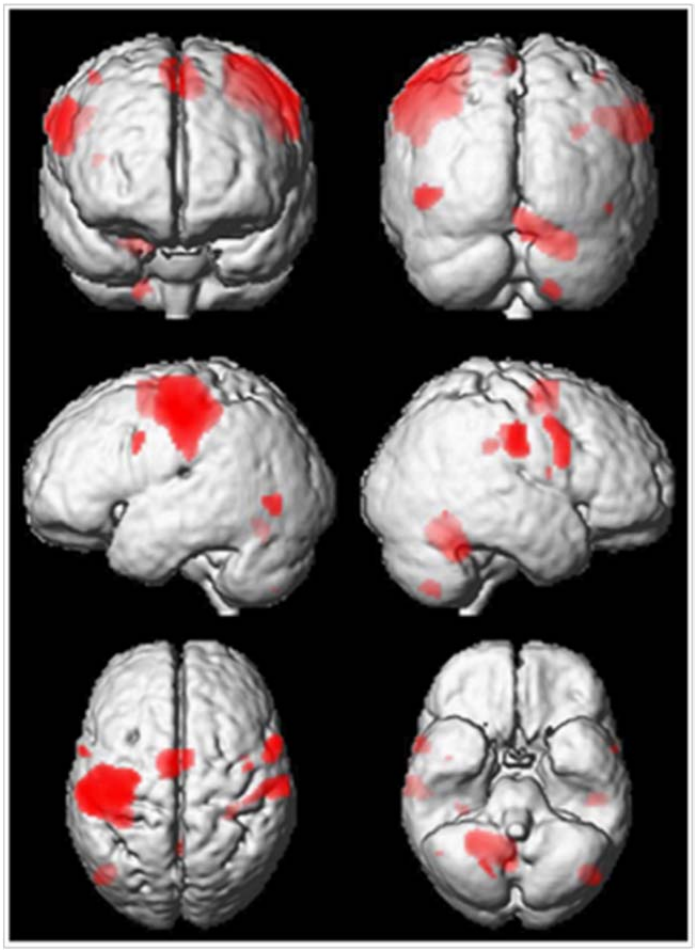


Figure 6. Significantly active clusters for the conjunction between active conditions are superimposed on a three-dimensional rendering of the group mean anatomical image (T1-weighted).

Sensorimotor activity in the pre- and postcentral gyri was also seen in regions ipsilateral (right hemisphere) to the active hand. In addition, clusters of active voxels were seen in the supplementary motor area (SMA) and in the ipsilateral cerebellum. The results from the conjunction analysis between active conditions largely replicated the findings from previous studies on the neural correlates of precision grasping, and are displayed in Figure 6.

The histograms in Figure 7, illustrated on a group mean normalized T1w image, show the mean adjusted BOLD response from local maxima of motor related activations during the four different conditions, with the mean activity during rest used as baseline. An overlap (yellow, Figure 7) in activation between the main effects was found in the right ipsilateral cerebellum, in lobule VI, and in the left contralateral lobule VI. Apart from this overlap the clusters of activations for the contrast high instability versus low instability and high force magnitude-low force magnitude were spatially separated. No significant interaction effects were found. This means that the combination of high instability and high force magnitude did not load synergistically (i.e. in a non-additive way) on any region.

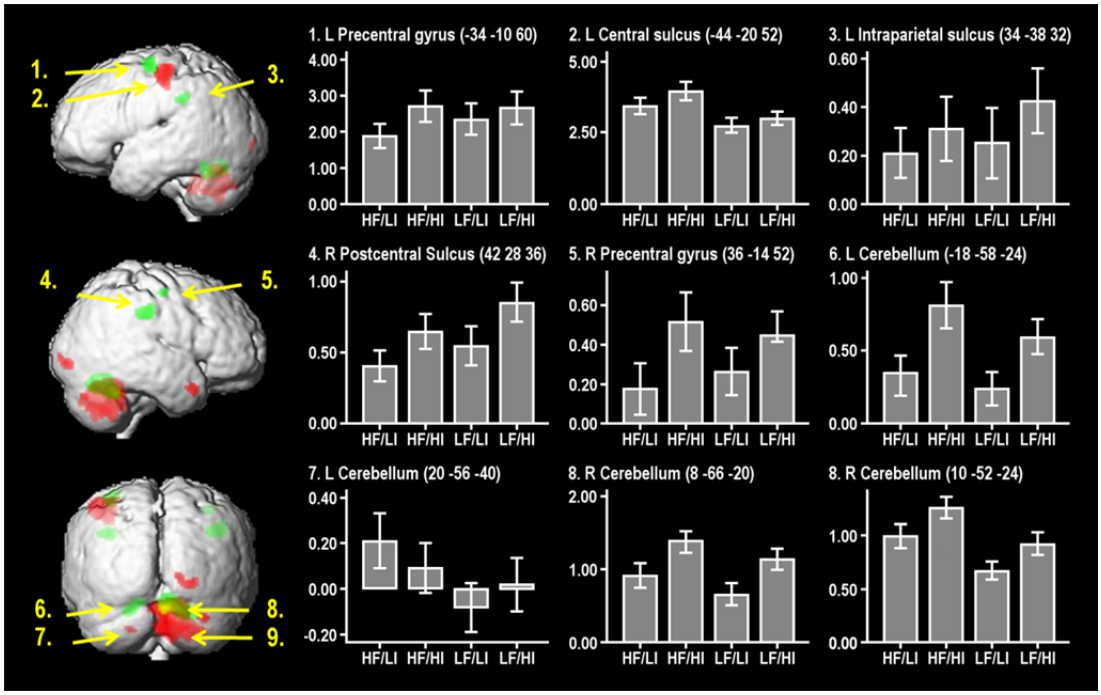


Figure 7. Fitted responses of active conditions in peak voxels reported in the main effects analysis (Force and Instability). Regions active in relation to High-Low Instability (green), High-Low Force magnitude (red), and regions which are active for both contrasts (yellow). Values on Y-axis represents mean adjusted BOLD response from local maxima of motor related activations during the four conditions, with the mean activity during rest (set to zero) used as baseline., X-axis represents the four conditions, T-bars represent +/-1 SE of percent signal change induced by each of the individual active conditions. L=left, R=right.

By using springs with different levels (high-low degree of challenge) of force constant and instability it was possible to investigate regions primarily associated with either generation of force or finger coordination during precision gripping, within one task, controlling for sensorimotor processing common to all springs. A conjunction analysis of the active conditions was performed to illustrate increases in activity common to all conditions. The largest cluster of activation includes primary and secondary sensory motor regions contralateral (left hemisphere) to the active hand.

In conclusion, this study not only confirms a recently described bilateral fronto-parieto-cerebellar network for manipulation of increasingly unstable objects, but also extends our understanding by describing its differentiated modulation with force magnitude and instability requirements.

4.3 STUDY III

The aim of Study III was to investigate the relationships between brain lesion characteristics, motor projection pattern and function in the hemiplegic hand.
A large spectrum of brain abnormalities was seen on MRI, including white matter damage of immaturity (WMDI), focal infarction, and maldevelopment. Reductions in the size of the basal ganglia or thalamus were observed in the context of all three lesion types (Figure 8).

Patterns of motor projection to the hemiplegic hand were contralateral (n=5), ipsilateral (n=5), or mixed (n=6). The most favourable hand function was seen in children who had white matter damage of immaturity with mild white matter loss and contralateral motorprojections. The most impaired hand function was seen in the ipsilateral motor-projection group. The finding that ipsilateral projections are associated with poor outcome is in line with previous research. However, there was a wide range in ability within this group (AHA 29-59%) indicating a fairly good assisting hand i.e., the hand functions well in bimanual activities, despite of the ipsilateral projection pattern. The projection pattern groups and performance on the B&B test are displayed in (Figure 9).

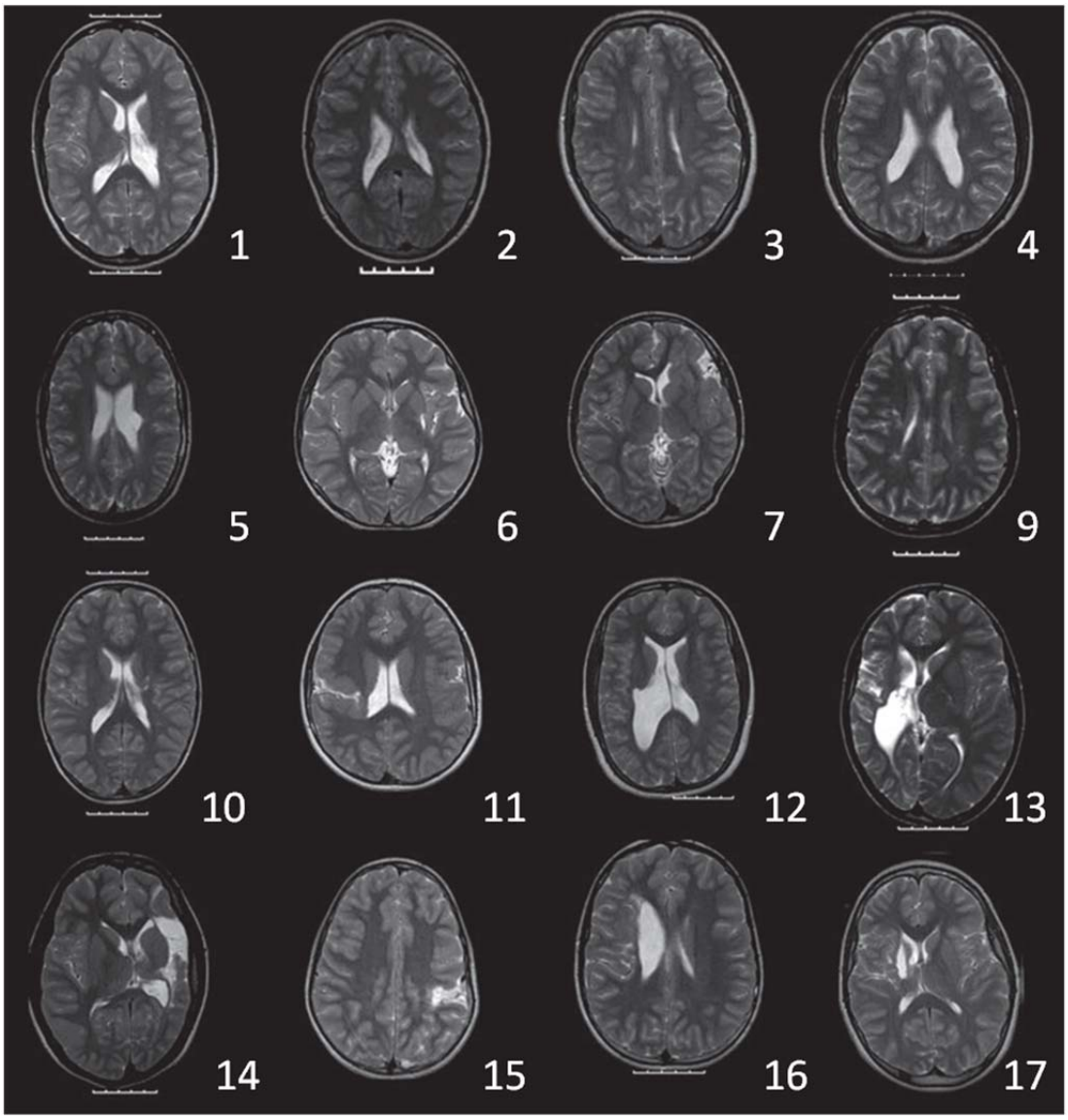


Figure 8. Axial slices showing each participant's lesion on T2-weighted magnetic resonance imaging. (MRI-data was not available for participant 8).

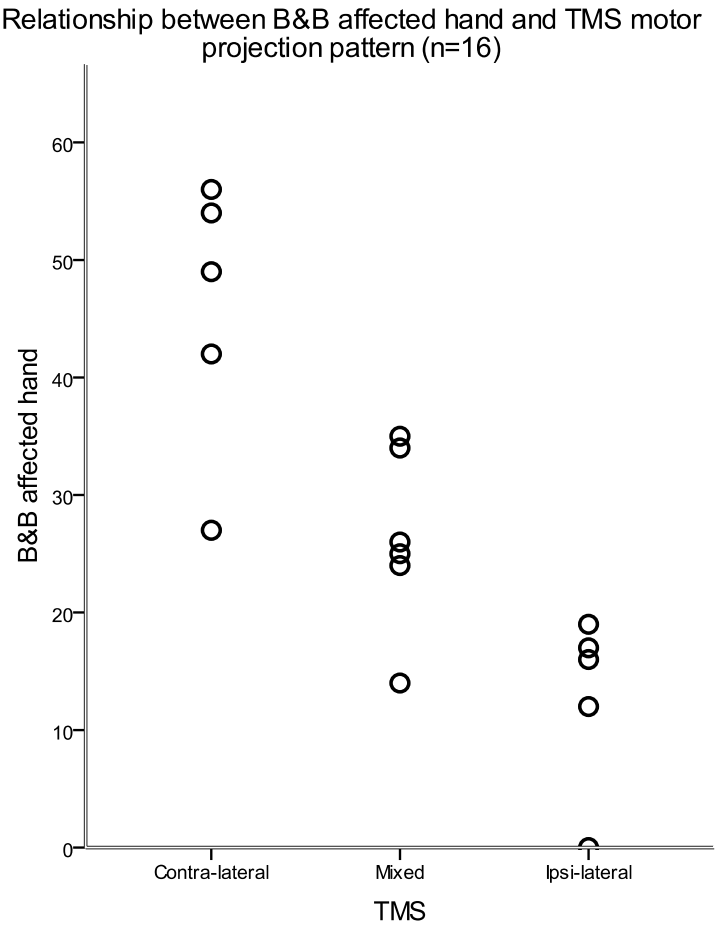


Figure 9. Relationship between the number of blocks moved in 60 seconds using the hemiplegic hand (B&B test; y axis) and the motor-projection pattern to the hemiplegic hand (assessed using TMS; x axis).

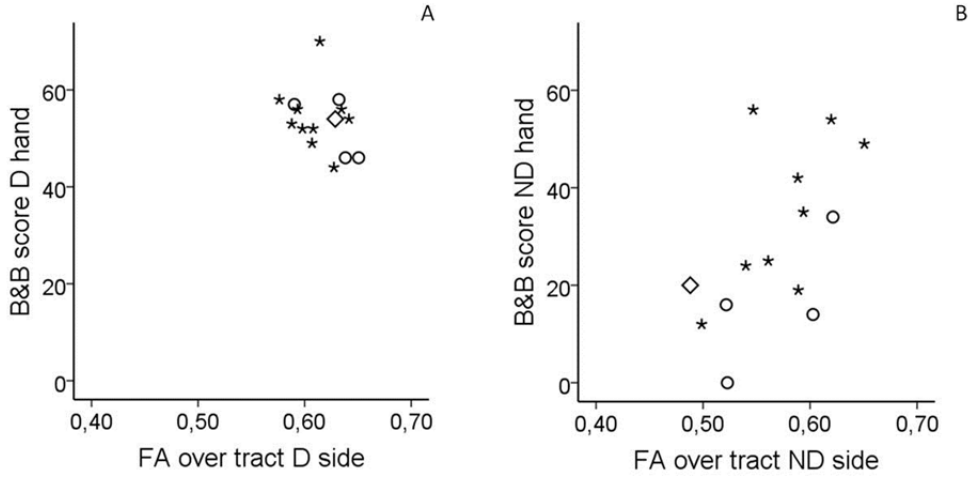
This study showed that the combined information from structural MRI and TMS can improve prediction of hand function. It was found that the combination of lesion type, location and extent was a stronger predictor of functional outcome than lesion type alone. Motor projection patterns appeared to be influenced by lesion extent and location, but not by lesion type. In addition, the findings suggest that children with ipsilateral projections can develop fairly good hand function and this has not previously been reported and is important information for treatment planning.

4.4 STUDY IV

The aim of the last study of this thesis was to investigate whether the variation in hand function that we found within each lesion type group in Study III could be further explained by changes in the microstructure of the corticofugal fibers as measured by diffusion MRI.

Significant differences in FA between the CP group and the control group were seen in both ROIs and the partial tract contralateral to the non-dominant hand. This was caused by an increase in D⊥, i.e. diffusivity perpendicular to the tract.

There was a significant positive correlation between FA in the partial tract contralateral to the non-dominant hand and test performance with the non-dominant hand. In contrast, for FA contralateral to the dominant hand and test performance with the dominant hand, no significant correlation was seen (Figure 10 A-B). Explorative regression analyses suggest that this was independent of lesion type or voxel number in the individual tracts or ROIs.



Figur 10 A-B. Relationships between functional outcome and FA. Performance on the B&B test (the higher the score, i.e. the more blocks moved within 60 seconds, the better the performance), D hand = dominant hand, ND hand = non-dominant hand, and association with FA, D side=tract contralateral to dominant hand, ND side = tract contralateral to non-dominant hand; n=15 children with CP.

The results of the analysis indicated a higher MD and lower FA in both ROIs and the partial tract on the affected side in comparison to the non-affected side in the children with CP. The same pattern, higer MD and lower FA in ROIs and partial tract contralateral to the non-dominant hand, was also found when compared to the corresponding measurements in controls.

The overall findings from this study indicate that diffusion MRI provides additional information to visual analysis of conventional structural MRI about structural changes in corticofugal fibers in children with unilateral CP. Fractional anisptropy in corticofugal fibers in the partial tract on the affected side correlate with performance on the B&B test in the non-dominant hand in the children with unilateral CP. The findings from this study are of clinical significance since they indicate that using FA may improve early prediction of outcome which is likely to be useful in planning of early intervention trials.

5 GENERAL DISCUSSION

5.1 ASPECTS OF VALIDITY

The findings from Study I indicate that the SD-test measures a unique latent trait that probably represents the ability to coordinate fingertip forces. This is perhaps the most interesting and important finding from this study since there are no other clinical tests available that capture this ability. Although promising, this work is to be regarded as an initial step in the development of the SD-test for children with CP. When evaluating evidence of validity it is of great importance to keep in mind that validity is never a property of a test, rather it should be seen as the property of test-scores when obtained with a measure and used for a specific purpose in a particular group of respondents (Goodwin 2002a; Goodwin 2002b). This means that the SD-test needs to be administered and evaluated in large groups of children with different types of CP before it can be claimed to be a clinical useful tool in this population. There are also other aspects of validity that need to be considered during the development of a new measurement tool, such as evidence based on relations to other variables and evidence based on response processes (American Educational Research Association 1999; Goodwin 2002a).

In Study I it was found that measures from the SD-test share variance with both the B&B test and pinch strength. This was an expected finding since both these measures require the formation and use of a precision grip. However, neither of these tests were specifically designed to capture fingertip force coordination which is the intended use for the SD-test. To more thoroughly investigate to what extent the SD-test measures the trait it is intended to measure, the test needs to be administered in larger samples of children with impaired hand function as well as typically developing children, and the results should be compared to other tests and assessments of manual dexterity that capture developmental changes as well as impairments in the ability to coordination of fingertip forces.

In Study I we report that performance on the SD-test, B&B test and measure of pinch strength improved with age. In addition, we found that improvements with age were also seen in the non-pinch strength-related variance of the SD-test, which presumably reflects dexterity. Longitudinal studies that follow the same individual over time are needed to further explore the developmental course of this ability.

In addition to this the reliability, or reproducibility, of the test when administered in specific populations needs to be determined together with the responsiveness to change, if the test is intended to be used not only as a descriptive tool but also a an outcome measure following intervention (Krumlinde-Sundholm 2008).

5.2 NEURAL CORRELATES OF UNSTABLE OBJECT MANIPULATION

One way of further stressing the question of the specific contribution of active brain areas during precision gripping, is to make the precision grip task more demanding by using an unstable object for manipulation. It can be hypothesized that this would require more on-line adjustments from the sensorimotor system which would make it possible to separate and highlight the contribution of areas involved in force magnitude or directional force control rather than areas mainly involved in the production of the movement per se.

The novelty of Study II lie in that we were able to independently vary the required magnitude of fingertip force and the instability requirements (i.e. the dynamical control of direction of fingertip force vectors) within the same task, while controlling for other factors common to all conditions.

The results of Study II can be compared to the previously mentioned investigation by Milner et al., who also investigated the neural correlates of manipulation of mechanically unstable objects (Milner et al. 2006). One important methodological difference concerns the objects used for manipulation. The mechanical construction of the unstable springs makes it necessary for the participant to constantly coordinate and adjust the forces produced, throughout the movement, to achieve a successful compression. Our task thus requires in-hand manipulation and coordination during a dynamic movement, in contrast to the tasks used by Milner et al., (2006) where the subjects were instructed to keep an unstable object in equilibrium, aiming at keeping the precision grip as static as possible. Although the task constraints are arguably quite different and the tasks can be hypothesized to at least partly load on different neural processes, the results from the Milner study (2006) and Study II are very similar with regard to activated brain regions. The combined results from the present study and the two studies by Milner et al*.,* (Milner et al. 2006; Milner et al. 2007) thus further strengthen the role of particularly the cerebellum during skillful manipulation of mechanically unstable objects.

Areas in the region of the intraparietal sulci and cerebellum have previously been suggested to be associated with the implementation of internal models (Bursztyn et al. 2006; Ehrsson et al. 2002; Kawato et al. 2003) that are of crucial importance for successful object manipulation when the task is difficult and requires a lot of on-line

adjustments of movements (Flanagan et al. 2006; Flanagan and Wing 1997; Kawato 1999; Ohki et al. 2002). Cerebellar involvement in skillful manipulation and error correction has also been highlighted in a recent study by Tanaka et al. (2009). The aim was to investigate the central representation of internal models for automated force production at fast and slow movement rates, at either 0,4 or 0,8Hz. Tanaka et al. found that the left cerebellum, showed stronger activation at the slow movement rate, and that there was a strong linear relationship between individual errors and activity in the cerebellum at both movement rates. The author suggests that increased cerebellar activation is not needed when the task is well learned/automatically performed and errors do not occur (Tanaka et al. 2009). We used a movement rate of 0,5Hz, i.e. close to the slow rate used in the Tanaka study, in Study II. Our paradigm was not designed to study error correction, and the subjects always managed to complete the task, but we did expect to see increased activity in brain areas related to movement correction during the compression of the unstable springs. Based on the finding by Tanaka it can be argued that the activity seen in the left cerebellum in our study is mainly related to continuous movement correction during task performance, which should be greater during the high instability conditions. This interpretation is further supported by that the corresponding region is not found active during all conditions in the conjunction analysis of Study II, i.e. the activity was not related to the movement rate across conditions in this experiment.

The increased brain activity associated with the high force–low force constant in Study II was found in the left primary motor regions, central sulcus and bilateral cerebellum. These results are also in line with previous findings regarding the close relationship between force magnitude production and activity in M1 (Ehrsson et al. 2003; Ehrsson et al. 2000; Ehrsson et al. 2001; Gallea et al. 2005; Kuhtz-Buschbeck et al. 2001). The activity in M1 was stronger during the compression of the stiffer springs, and this is probably a reflection of the increased number of hand and fore arm muscles recruited during this task. Thus, the current findings further support the results of Milner et al. suggesting that the features of object manipulation dynamics during manipulation of mechanically unstable objects is unlikely to be located in M1 (Milner et al. 2006; Milner et al. 2007). This is also suggested by Dafotakis et al., who showed that TMS stimulation over M1 did not disrupt reactive adjustments of grip force during object manipulation (Dafotakis et al. 2008).

The results of Study II are compatible with a recent fMRI study investigating brain activity during compression of springs with constant force requirements but varying instability requirements (Mosier et al. 2011). In addition to increased activity in the bilateral frontal-parietal-cerebellar network during compression of more unstable springs, they noted increased activity in basal ganglia that was not found in the present study. This is an interesting finding since the basal ganglia have been shown to

be important for different aspects of precision grasping (see review by (Prodoehl et al. 2009).

The results of Study II show that the cerebellum can play different roles in the sensory motor network active during precision gripping of unstable objects depending on whether the task primarily requires control of force magnitude or force direction.

5.3 RE-ORGANIZATION OF MOTOR PROJECTION PATTERNS IN UNILATERAL CP

The results from Study III showed that the most favourable hand function was seen in children who had WMDI with mild white matter loss and contralateral motor projections while children with ipsilateral projections had the most impaired function. Motor projection patterns appeared to be influenced by lesion extent and location, but not lesion type.

The perhaps most interesting finding from Study III is that children with ipsilateral projections to the affected hand could have fairly good hand function. This was illustrated by a wide range in AHA-scores indicating a rather well functioning assisting hand in some of the children within this projection pattern group. We do not know if this variation in function should be seen as a result of typical development in children with unilateral CP, or as an effect of long term treatment programmes. Nevertheless, this information is likely to be of importance for treatment planning and prediction of hand function outcome in young children.

As outlined in the introduction of this thesis, ipsilateral motor pathways are part of typical development and most of them can be expected to withdraw with time when not used (Eyre 2007; Martin 2005). However, when a unilateral brain lesion occurs and disrupts the typical course of development it is possible that these ipsilateral projections persist (Staudt 2010). Eyre and colleagues (Eyre 2007; Eyre et al. 2007) have presented evidence that suggests that this type of re-organization should be considered to be a result of activity-dependent competitive withdrawal of contralateral projections from the affected cortex, rather than a reparative compensatory mechanism (Eyre 2007; Eyre et al. 2007). An important point made by Eyre et al., is that the loss of MEPs is not necessarily due to the loss of corticospinal axons. The loss of MEPs could also be a result of an increase in motor threshold that exceeds the maximum TMS stimulator output (Eyre et al. 2007).

There have been no reports of normal hand function in children with unilateral CP and ipsilateral motor projections from the unaffected hemisphere (Staudt 2010). This together with ongoing development of the the corticospinal system during the first

years of life raises the question of whether or not this phenomenon could be avoided through intervention and, if so, lead to a more favorable outcome as, for example, suggested in a review by Eyre et al. (Eyre et al. 2007).

Another important question is how the presence of ipsilateral projections affect treatment outcome and whether this is something that therapists need to take into consideration when planning interventions. Most children with unilateral CP participate in extensive treatment programs aiming at improving upper limb function throughout childhood and adolescence. Modified Constraint Induced Movement Therapy (mCIMT), has been shown to have significant treatment effect in a single trial (Hoare et al. 2007). This type of therapy is based on restriction of the dominant hand, with aid of a mitten, a cast or a splint, while the affected hand receives intensive massed practice.

Kuhnke et al. investigated if patients with unilateral CP and ipsilateral corticospinal projections responded differently to CIMT than patients with contralateral projections to the affected hand. The authors found that patients in both groups improved with regards to quality of movements, as assessed by the Wolf motor function test, but that only the participants with typical motor projection pattern improved on movement speed. However, it should be noted that the differences in speed were rather small and it is uncertain whether this is of clinical significance (Kuhnke et al. 2008). The same research group also published a paper combining TMS and fMRI results following CIMT therapy in a subgroup of patients with perinatal stroke (middle cererbral artery infarcts) and intact crossed corticospinal projections to the affected hand (Walther et al. 2009). Here the authors found a significant increase in MEP amplitudes recorded from the paretic hand as well as an increased activation of the contralateral primary and supplementary motor areas in the affected hemisphere during active hand movements (Walther et al. 2009).

The findings from this thesis, together with the findings from the studies described above and in the introduction indicate that TMS, alone or in combination with fMRI, is a method that can be successfully used to study the organization of the healthy motor system and also after early acquired brain lesions, and that the information obtained from this method can be of importance for outcome in children with unilateral CP.

5.4 DIFFUSION MEASURES IN RELATION TO HAND FUNCTION IN UNILATERAL CP

In Study IV, we found that children with CP had significantly lower FA in both ROIs and the partial tract corresponding to the affected hand when compared to controls. FA in the partial tract correlated with scores on the B&B test, and this was independent of lesion type. The study group in Study IV included children with a range of lesion types including, WMDI, focal infarct and maldevelopment. This can be considered a strength of the study because we, irrespective of the primary underlying injury/lesion that caused the clinical phenotype of unilateral CP, we found differences in diffusion measures between the children with CP and the controls. In addition, the correlation between the hand function measure and FA in the corticofugal fibers was similar across lesion types, which suggests that FA in the corticofugal fibers is a useful marker of damage to the CST and correlates with hand function.

Our findings are in line with another recently published study that also focused on the associations between hand function and diffusion measures (Bleyenheuft et al. 2007). The authors of this study report that measurements of the cross-sectional are of the cerebral peduncles on T1-weighted MRI resulted in an underestimation of the CST tract dysgenesis and that diffusion measures correlated more strongly with clinical measures of hand function (Bleyenheuft et al. 2007).

It is not uncommon to find bilateral lesions on visual inspection of MRIs in children with CP presenting with unilateral motor deficits (Niemann et al. 1996; Wu et al. 2006), and this was indeed the case in Study IV. In the children with CP, we found significant differences in diffusion measures between the two hemispheres, not only in those with unilateral lesions (as assessed on visual inspection of MRI) but also in those with bilateral abnormalities on visual inspection of MRI. Interestingly, the same pattern of lower FA and higher MD in the tract contralateral to the hand that was most impaired in function was also found in those with bilateral lesions. Therefore, we conclude that diffusion measures provide a more sensitive measure of tract injury than purely visual inspection of T1-weighted and T2-weighted images.

Study IV is a cross sectional study and prospective long term studies in larger populations of children with unilateral CP are needed to confirm our results and conclusion. Nevertheless, our findings show that diffusion MRI provides additional information to visual analysis of conventional structural MRI about structural changes in corticofugal fibers in children with unilateral CP and importantly, that diffusion measures correlate with measures of hand function. Since FA can be measured at an early age when it is difficult to perform detailed clinical assessments of hand function, diffusion measures can be a useful tool for early prediction of outcome and also for

planning and evaluation of intervention aiming at improving hand function. These assumptions are supported by two recent studies which indicate that diffusion measures obtained at young age indeed correlate with later overall motor outcome in children with motor dysfunction (Drobyshevsky et al. 2007; Ludeman et al. 2008). Ludeman and colleagues, showed that children who later in life were diagnosed with permanent motor dysfunction had lower FA and higher transverse diffusivity at age less than 30 months, compared to children in whom the motor dysfunction normalized (Ludeman et al. 2008).

5.5 METHODOLOGICAL CONSIDERATIONS

As previously described the results of Study II are compatible with a recent fMRI study investigating brain activity during compression of springs with constant force requirements but varying instability requirements (Mosier et al. 2011). However, we did not find the same increase in activity in the basal ganglia during compression of the more unstable springs as the authors of this study report.
Whether or not this is related to the differences in the tasks used, study design or analysis of results is difficult to say. It is likely that the four springs we chose were not equally difficult for all subjects. In a future experiment, it would be interesting to use the same study design, but choose individual springs for each subject. This would make it possible to maximize the difference between springs while also making the task as difficult as possible for each individual and by doing so further elucidate both cortical and sub-cortical parts of the grasping network involved either control of force magnitude or force direction.

The sample size in the studies including children with unilateral CP, Study III and IV, was fairly small and this can of course be seen as a limitation and make it difficult to draw general conclusions from the results of these studies. However, the children included in these studies showed a wide range in hand function as well as in lesion types that can be considered representative of the population of interest. Moreover, since the results show relationships between lesion characteristics and hand function, despite the great inter-individual differences within the sample, the results are likely to apply to children with unilateral CP in general and this makes our findings clinically relevant.

Transcranial magnetic stimulation is not a method that is commonly used to predict motor outcome in clinical practice today. The method has been successfully used in research for years, and there have not been any reports of serious side effects associated with the method in children. This makes TMS a promising tool that could be used in conjunction with the established assessments already used today, for review please see Garvey et al. 2004 or Frye et al. 2008 (Frye et al. 2008; Garvey and

Gilbert 2004). All children that participated in Study III tolerated the TMS examination well and no one reported any discomfort during or after the examination.

In Study IV we used ROI- and tract-based diffusion measurements. Defining ROIs unavoidably introduces an observer bias in the analysis and this method requires that the voxels included in the analysis represent corresponding fibers. We addressed this by defining individually sized ROIs based on their anatomical extent. In addition to this, we deliberately limited tracking of the corticofugal fibers to the part between the internal capsule and cerebral peduncle, aiming at including all motor projections and ensuring a single dominant fiber population in the tract so that the voxel values represent meaningful tensor measures and to avoid the issue of crossing fibers of the thalamic radiation and the superior longitudinal fascicule which makes tracking above the internal capsule difficult.

5.6 CLINICAL IMPLICATIONS AND CONCLUSIONS

The overall clinical implications and conclusions from this thesis are that combined information from TMS, visual inspection of conventional structural MRI and the use of quantitative measures from diffusion MRI can improve our ability to predict hand function in children with unilateral CP. The findings illustrate how the large inter-individual variations seen in hand function within this group of children can be attributed to a number of different factors, such as lesion location and extent, microstructural alterations in the corticospinal tract and motor projection pattern to the affected hand, and that all these aspects should be taken into consideration when attempting to predict hand function in young children who have suffered an early insult to the brain leading to the clinical presentation of unilateral CP.

The SD-test, although still requiring further development to be a clinical useful tool, offers the possibility to, in a clinical setting, capture an important aspect of dexterous fine motor control that is essential in many everyday tasks and often impaired in children with CP. This is important since there are no other clinical tests available that measures this ability.

The SD-test also provides an interesting concept that can be used to study the neural correlates of the ability to control magnitude and direction of fingertip forces. Study II gave insight into how the brain controls these two different aspects of dexterous manipulation in adults with no neurological impairments. The knowledge of how the brain controls dexterous manipulation provides a basis for future research on how this ability is organized in the brain following early acquired lesions and how the re-organization is related to hand function.

6 FUTURE DIRECTIONS

In retrospect there are, of course, many things I would do differently today if I were given the chance to re-do the studies included in this thesis. But, if I were to do the same studies over again, I would not be able to see the things I should change, nor would I be able to see the things I should not change, without the experience I have gained during the years as a PhD student.

Working on these four studies, I have been provided with the opportunity to at least begin to learn how to use some advanced neuroimaging and neurophysiological techniques in combination with assessments of hand function to study the relationships between brain structure and function and motor skills. This has generated a number of new research questions and project ideas in which these methods are combined. A long-term goal with this line of research would be not only to improve our ability to *predict* outcome but also our ability to *improve* outcome and tailor treatment to the individual needs of each child.

To move towards this goal it would be a very interesting, and also challenging, task to investigate how parameters obtained from the different methods used in this thesis (TMS, conventional structural MRI, DTI and fMRI) influence outcome of intensive training of fine motor skills in children with unilateral CP.

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