Sensorimotor Behavior in Children Born Preterm and Adolescents with Cerebral Palsy

Side preference, movement organization, and training

Anna-Maria Johansson
To my loved ones ♥
ACKNOWLEDGEMENTS

The past few years have been an inspiring and exciting time where I have had the opportunity to work and develop in a stimulating research environment. There are several people and instances that have enabled the making of this thesis and contributed to making these years such a special time.

I would firstly like to thank all the families, children and adolescents for partaking in the studies. Without you there would be no thesis.

My supervisors Louise Rönnqvist and Erik Domellöf, thank you for your excellent advisory skills involving lots of encouragement and support. I greatly value your openness, good humor, go-for-it attitude, and your willingness to share your experience and expert knowledge. You make a great team!

Without funding, of course, there would be few opportunities to endeavor into a research career. I would like to thank the Norrbacka-Eugenia Foundation for funding my Ph.D. studies and the Swedish Research Council for their contribution to the projects.

Special thanks to Aijaz Farooqi and Magnus Domellöf for your advice and collaboration in the data collection. I would also like to thank Jennie, Johan, Henrik, Kalle, and Helena for your assistance in the projects.

I am also very grateful for the invaluable comments and suggestions for improvements on earlier work and drafts of this thesis from Gustaf Gredebäck, Anna-Sara Claeson, Anna Stigsdotter-Neely, Linus Andersson, och Kerstin Rosander.

During my time as a Ph.D. student I have been at the MRI clinic at the Norrlands’ University Hospital collecting data for the projects involved. Although these results did not make it into the thesis I am nevertheless grateful to the staff at the clinic for your kind assistance. A special thanks to our collaborators in the research focused on imaging; Katrine Åhlström Riklund, Richard Birgander, Thomas Lindeqvist and Niklas Lenfeldt.

I have also made many friends at the Department of Psychology. Carola, Petra (who among many other things happens to be the best roomie ever!), Camilla, Daniel, Inga, Eva, Helene, Mikael S, Esther, Olympia, Susanne and
Linus. Thank you all for the good times. You are an important reason for why these years have been so much fun!

I would like to thank my family and friends for your love, support, and patience with my, at many times, both physical and mental absence. A very special thank you to Henrik for designing the cover of the thesis, producing the included photographs, great work with movement data processing, pizza evenings with you and your girls, and of course for being a great brother. Darling Ella, thank you for lending us a hand with the cover and for letting me use your photographs. To Lars, the co-founder of project JJ, thank you for blessing my life with your presence!

Umeå, October 2012
# TABLE OF CONTENTS

## ACKNOWLEDGEMENTS ii
## TABLE OF CONTENTS iv
## ABSTRACT vii
## SAMMANFATTNING PÅ SVENSKA ix
## ABBREVIATIONS xiii
## LIST OF PAPERS xiv
## INTRODUCTION 1

- Preterm birth and CP 1
- Demographics 1
- The vulnerable preterm brain 3
  - Maturational aspects 3
  - Biological mechanisms 3
  - Lesion types and their effect on brain development 4
- Genetic factors 6
- Sensorimotor and intellectual function in children born preterm 7
- General motor functions and the relation to risk factors 7
- Intellectual function in children born preterm 9
- Relations between motor function and cognition in children born preterm 11
- Upper-limb goal-directed movements in children born preterm 12
- Handedness and movement performance in children born preterm 13
- Cerebral Palsy 15
  - Functional impairments in children with CP 15
  - Risk factors for the development of CP 17
  - Brain lesions in CP 17
  - Goal-directed upper-limb movements in CP 18
  - The malleable brain 19
    - Plastic changes in development 19
    - Plasticity and interventions 19

## OBJECTIVES 21

## METHODS 22

- Systematic review and meta-analysis (study I) 22
- Study design and inclusion criteria 22
- Quality assessment 22
- Statistical methods 23
- Empirical studies (studies II-IV) 25
- Study designs 25
  - Handedness, movement performance, and intellectual function in children born preterm (studies II and III) 25
  - Short- and long-term effects of timing and rhythmicity training on upper-limb movements in children with cerebral palsy (study IV) 25
Participant description and recruitment process (study II-IV) 26
Studies II-III 26
Study IV 28
Methods of assessment 29
Frequency assessment of hand dominance (studies II and III) 29
3-dimensional motion analyses (studies II-IV) 30
Interactive Metronome (study IV) 35
Gross Motor Function Classification System (Study IV) 38
Manual Ability Classification System (Study IV) 38
Arm/hand function questionnaire (study IV) 39
Socioeconomic information (studies II-III) 40
Wechsler's Intelligence Scale for Children (study III) 40
Journal background/ medical birth history (studies II-IV) 40
Statistical methods 41
Study II 41
Study III 42
Study IV 42
Ethical considerations 42
SUMMARY OF RESULTS AND BRIEF DISCUSSION OF FINDINGS 43
Study I 43
Study II 46
Study III 50
Study IV 52
GENERAL DISCUSSION, FUTURE PROSPECTS AND CONCLUSIONS 56
Differences between the groups of children born preterm and fullterm 56
Hand preference 56
Movement organization 57
Intellectual function 58
The influence of age, GA, and sex 59
Handedness: a dichotomy between preference and performance? 60
Training of sensorimotor functions 61
Timing training and constraints 61
Feedback in sensorimotor learning 62
Motor planning or biomechanical constraints? 62
Methodological considerations 63
Future prospects and conclusions 64
The role of intellectual function in movement organization 64
The role of sensory and proprioceptive information in movement organization 65
The role of larger study populations 66
The advancement of synchronized metronome training studies 66
REFERENCES 67
ABSTRACT

Preterm birth (< 37 complete gestation weeks, GWs) is the single most prominent risk factor for the development of cerebral palsy (CP). This is due to the immature physiological state of the preterm born infant which increases the risk of brain lesions. In CP, prominent sensorimotor, cognitive, and perceptual deviations are manifested with varying degrees of functional impairment. Although the majority of children born preterm (PT) do not develop CP, sensorimotor and cognitive deficits are frequently reported in the absence of major disability. To date, few studies have focused on detailed kinematic analysis of upper-body goal-directed movements and how aspects of movement organization and control are related to hand preference, intellectual function, gestational age, and sex within groups of prematurely born children. Further, studies evaluating effects of sensorimotor training in persons with CP is needed and of importance as positive effects on movement performance may increase individual autonomy as a consequence.

To investigate the prevalence of non-right hand preference within children born PT in comparison to children born fullterm (FT), a meta-analysis and literature review were performed (study I). It was shown that children born PT had increased rates of non-right handedness (NRH) corresponding to 22% compared to 12% in the FT group (odds ratio 2.12). In study II, hand preference and side specific movement performance in children born PT (≤ 35 GWs) compared to an age matched group of children born FT were investigated. All included participants were 4-8 years of age without major disability. Movement performance was studied through detailed kinematic registrations of the head, arm, and hand during a goal-directed task and hand preference through observations of the hand used when manipulating different objects. On a group level, the children born PT, specifically those born < 33 GWs, showed an increased rate of NRH, weaker strength of hand preference, and a lack of side specificity in terms of movement kinematics. In general, the children born < 33 GWs also displayed poorer movement organization and control as expressed by longer durations, less smooth and longer distances of the movement trajectories. These findings imply that preterm birth has long term effects on sensorimotor organization and function, possibly reflecting a developmental delay and/or a persistent effect that may be associated with the increased risk of deviations in brain development.

In study III, associations between movement performance, assessed with the same task as in study II, and intellectual function (Wechsler Intelligence
Scale for Children, 4th ed; WISC-IV) were studied. This study included a subsample of the children from study II at 6-8 years of age. The results showed a link between movement organization and general intellectual functioning (IQ), when controlling for effects of GA and sex, for the PT born but not the FT born children. These findings suggest shared neural underpinnings and interrelated development of motor and intellectual functions.

In study IV, kinematic analysis of upper-body movements and subjective experience of change in upper-body function were applied before and after a period of synchronized metronome training (SMT) in adolescents with varying degree of CP to study the effects of this type of training. The SMT method applied entailed elements of movement timing and rhythmic activation coupled with feedback and was hypothesized to train sensorimotor integration. It was found that SMT did improve, to varying degrees, the organization and control of movements in adolescents with CP. The participants with more severe forms of CP reported substantial effects in daily living activities. The observed effects of SMT warrant further study of specific effects on movement planning, biomechanical constraints, and attention.

The relation between hand preference and movement performance, movement performance and intellectual function, and aspects related to the SMT method applied in study IV are considered. Specifically, the lack of side specific movement organization within the group of children born PT is discussed from perspectives of motor learning, plasticity, and genetics. Further, the relations between movement performance and intellectual functions are considered and suggestions for how this association could be tested are given. With relation to study IV, the functions trained by the specific SMT method applied and the accessibility of individuals with different degree of CP is discussed. Methodological considerations, suggestions for methodological refinements and the development of research paradigms aimed at the investigation of proposed new lines of enquiry are presented.
SAMMANFATTNING PÅ SVENSKA

Varje år föds det drygt 100 000 barn i Sverige. Cirka 5% av dessa barn föds för tidigt, det vill säga före 37 kompletta graviditetsveckor. Av de barn som föds för tidigt har majoriteten en gestationsålder (antalet graviditetsveckor) över 33 veckor (Medicinska födelseregistret, 2009). Omkring 8% av barn som föds för tidigt diagnosticas senare med cerebral pares (CP) (Ancel, et al., 2006) och omkring hälften av personer med diagnosen CP har en för tidig födelsehistorik (Beaino et al., 2010). CP är ett paraplybegrepp som innefattar ett flertal icke-progressiva motoriska utvecklingsavvikelser av olika karaktär och funktionsnedsättningsgrad, orsakade av hjärnskador som inträffar under fosterlivet eller vid förlossningen. Vanligtvis så påverkas även sensorik, perception, kognition, och beteende negativt (Rosenbaum, Paneth, Leviton, Goldstein, & Bax, 2008). En prematur födsla utgör den största riskfaktorn för utvecklingen av CP där risken är störst för de barn som föds allra tidigast (Murphy, Sellers, MacKenzie, Yudkin, & Johnson, 1995). De allra flesta barn som föds för tidigt drabbas dock inte av grav sensomotorisk funktionsnedsättning som till exempel CP trots att det finns en ökad risk för hjärnskador hos denna grupp. Ett flertal studier har ändå visat att barn som fötts för tidigt och ej diagnosticerats med CP i högre grad än fullgångna barn generellt har både motoriska (e.g., Williams et al., 2010) och kognitiva (e.g., Bhutta, 2002) funktionsnedsättningar.

I dagsläget så har endast ett fåtal studier fokuserat på att i detalj studera organiseringen av målinriktade hand-armrörelser hos barn som fötts för tidigt. Av dessa har merparten fokuserat på spädbarn i syfte att finna tidiga markörer för sensomotoriska avvikelser. Då de sensomotoriska problemen hos för tidigt födda barn kvarstår i skolaldern och i vissa fall är så diskreta att de upp täcks först när barnet börjar skolan så kan rörelsevenalyser vara en metod som kan bidra till ökad förståelse och kunskap om hur den sensomotoriska påverkan uttrycks hos äldre barn. Ett av syftena med denna avhandling var således att noggrant studera organiseringen av huvud-, arm-, och handrörelser under en målinriktad handling hos barn som fötts för tidigt jämfört med en grupp barn i samma åldrar (4-8 år) som fötts efter fullgången graviditet. Av intresse är att studera relationen mellan aspekter associerade med rörelseorganisation och handpreferens, intellektuell förmåga, gestationsålder, samt kön. Då barn och ungdomar med CP utgör den största diagnosgruppen som behandlas inom barn- och ungdomshabiliteringar (Odding, Roebroeck, & Stam, 2006) finns det ett stort behov av att utvärdera effekten av redan existerande träningsmetoder. Ett ytterligare syfte med detta avhandlingsarbete var att utvärdera både kort- och långtidseffekter av en etablerad träningsmetod (synchronized
metronome training; SMT) som antas främja den sensomotoriska integreringen hos ungdomar (12-17 år) med diagnosen CP. Effekterna av denna träningsmetod utvärderades med hjälp av detaljerad rörelseanalys samt ett frågeformulär gällande individens upplevelse av förändring.


I studie III undersökt sambanden mellan intellektuell förmåga och organisationen av rörelser hos barn som fötts för tidigt samt hos barn som fötts efter en fullgången graviditet i 6-8 års ålder (en subgrupp ur studie II). Den intellektuella förmågan undersöktes med hjälp av Wechsler Intelligence

I avhandlingen diskuteras även relationen mellan handpreferens och kvalitet på rörelser i relation till den föredragna och icke-föredragna handen, samband mellan organisering av rörelser och intellektuell förmåga, samt aspekter relaterade till SMT metoden som applicerats i studie IV. Specifikt diskuteras avsaknaden av en sidospecifik rörelseorganisering hos gruppen barn som fötts för tidigt i relation till motorisk inlärning och hjärnans förmåga att förändra sig. Relationen mellan organisering av rörelser och intellektuell förmåga tas i beaktande och förslag på hur detta samband kan undersökas i kommande studier ges. Vidare så diskuteras vilka funktioner som SMT-metoden tränar samt dess tillgänglighet för barn och ungdomar med olika grad av funktionsnedsättning relaterad till typ av CP diagnos. Metodologiska överväganden och idéer för framtida forskningsansatser inom dessa områden presenteras.
ABBREVIATIONS

ANCOVA  Analysis of covariance
BW  Birth weight
CP  Cerebral palsy
CS  Corticospinal
ELBW  Extremely low birth weight, < 1000 gram
E-PT  Extremely preterm (< 28 GWs)
FT  Fullterm
GA  Gestational age, used interchangeably with GW
GM  Gray matter
GMFCS  Gross Motor Function Classification System
GW  Gestational week, used interchangeably with GA
IVH  Intraventricular hemorrhage
IQ  Intelligence Quotient
MACS  Manual Ability Classification System
M-PT  Moderately preterm (33-35 GW)
MU  Movement unit
MANCOVA  Multivariate analysis of covariance
OR  Odds ratio
PAM  Pacemaker-accumulator model
PVL  Periventricular leukomalacia
ROP  Retinopathy of prematurity
SGA  Small for gestational age
SMT  Synchronized metronome training
SVZ  Subventricular zone
VIQ  Verbal IQ
V-PT  Very preterm (29-32+6 GW)
WISC-IV  Wechsler’s Intelligence Scale for Children, 4th edition
WM  White matter
LIST OF PAPERS


*Papers I and IV have been reprinted with the permission of the copyright holders.*
INTRODUCTION

The main objectives of this thesis were to study sensorimotor behaviors in children born preterm and in adolescents with cerebral palsy (CP). The studies within the thesis are focused on the investigation of hand preference, side specific and general movement performance in children born preterm. An important aim was also to study effects of synchronized metronome training (SMT) on movement performance in adolescents with CP. Movement performance was studied by detailed kinematic analyses of upper-body (head, arm, and hand) goal-directed movements. Further, associations between movement organization, gestational age (GA), sex and intellectual function were studied in the children born preterm. Detailed measures and analyses of movement organization were undertaken in this endeavour.

The introduction to the thesis will provide a background to this area of research. Firstly, the associations between preterm birth and CP are presented from a demographic perspective. This is followed by a brief description of the neurobiological and maturational aspects that render the preterm born infant especially prone to brain lesions associated with CP. This section also provides neurobiological explanations for why children born preterm, without major disability, often show mild to moderate motor, cognitive, and behavioral impairments. A theoretical account of hand preference and a brief review of handedness within this group of children is also given. Secondly, a background to sensorimotor and intellectual functions and their relation in children born preterm without major disability is presented. Thirdly, a description is given of the functional motor impairments in CP and different CP diagnoses, associated brain lesions, and effects of interventions.

Preterm birth and CP

Demographics

Every year, just over 100,000 children are born in Sweden. Of these, approximately 5% are of preterm status (< 37 gestation weeks; GWs) where the majority (≈4%) of children are born after GW 33 (The Swedish Medical Birth Register, 2009). Over the past three decades, due to advancements in obstetric and neonatal intensive care, there has been considerable improvement in the survival rates of infants born preterm and/or with a low (< 2500 grams) birth weight (BW). The main rise in survival rates can be
observed in infants born < 26 complete GWs or at extremely low BWs (< 1000 grams, ELBW) (e.g., Colvin, McGuire, & Fowlie, 2004). The immature physiological state of the preterm born infant is associated with increased risk of disruption or lesions to the developing central nervous system. Preterm birth is the most prominent risk factor for the development of cerebral palsy (Murphy, Sellers, MacKenzie, Yudkin, & Johnson, 1995), which is a non-progressive disorder with persistent sensorimotor limitations and frequent deviances in cognition, perception, and behaviour caused by pre- or perinatal brain lesions (Rosenbaum, Paneth, Leviton, Goldstein, & Bax, 2008). Children with CP constitute the largest diagnostic group treated within pediatric rehabilitation services (Odding, Roebroeck, & Stam, 2006), thus, research approaches aimed at the development, evaluation, and improvement of training methods are necessary.

The prevalence of CP has been shown to be 1.5-2.5/1,000 live births (e.g., Cans et al., 2007; Himmelmann, Hagberg, & Uvebrant, 2010; Nordmark, Hägglund, & Lagergren, 2001). Although rates of premature birth are increasing in most countries (Blencowe et al., 2012), the incidence and severity of CP in preterm born populations have been shown to be decreasing (van Haastert et al., 2011). Within the population with CP in Sweden, 5.5% were born < 28 GWs, 4.4% between GW 28-31, and 0.15% were born > 36 GWs (Himmelmann et al., 2010). Within populations born preterm, the prevalence of CP has been estimated at approximately 0.7% at 34 GWs (Marret et al., 2007), gradually increasing with lowering of GA to 4% in GW 32, and at approximately 20% at 24-26 GWs (Ancel et al., 2006). This is to be compared to the prevalence of CP in the fullterm born population which has been estimated to 0.9 to 1.43/1,000 live births (Ancel et al., 2006; Himmelmann et al., 2010; Marret et al., 2007).

As shown, a relation between preterm birth and CP in terms of increased prevalence of CP in preterm born populations is clearly evident. It is also clear that the majority of children born preterm do not develop CP. However, school-aged children born preterm without major disability have been shown to have considerable cognitive, behavioral, motor, and neuromotor deficits (Edwards et al., 2011; Ment, Hirtz, & Hüppi, 2009; Williams, Lee, & Anderson, 2010; de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009). It has been argued that neuromotor abnormalities are the most common hidden disability among preterm children as they usually go undetected until school age (Bracewell & Marlow, 2002).
The vulnerable preterm brain

It is well known that the developing brain has different susceptibility to injury at different times in development, resulting in neuronal developmental disruption and/or necrosis that is dependent on the type of injury, time of occurrence in development, localization, and the extent of the insult (e.g., Ferriero, 2004; Johnston & Hoon, 2006; Rees & Inder, 2005; Volpe, 1998, 2009). The risk of such events occurring gradually increases with lowering of GA, which puts the infant born preterm at increased risk of suffering brain lesions (Volpe, 2008, 2009). At times the insult is so timed and of such magnitude that it results in more severe sensorimotor deviations as those seen in CP (Glinianaia, Rankin, & Colver, 2011).

Maturational aspects

The infant born preterm is specifically vulnerable to brain lesions due to an interaction between the pathological effects of neuro-destructive events and the developmental state of the infant. The lesions that occur in response to the neuro-destructive events are primarily located in the cerebral white matter (WM) as the vascular support of this area is underdeveloped and vulnerable. The immaturity of the cerebral vascular system increases the risk of oxygen deprivation and irregularities in perfusion pressure (Soul et al., 2007; Volpe, 1998, 2008). Further, the infant born preterm has a respiratory system that is underdeveloped, which adds to the risk of low oxygen saturation (Volpe, 2001). From the 24th GW the arteries in the WM undergo rapid development, where vascular interconnections are formed and as a result of this development the infant born preterm is less susceptible to more severe forms of WM insults after the 32nd GW (Johnston & Hoon, 2006). However, aspects of the cerebral vascular system are still immature at 40 GW and falls in perfusion pressure may therefore still cause WM injury in the moderately preterm and fullterm born child (Volpe, 2001). In terms of brain development, the period of 24-40 GW is a time of important developmental, often overlapping processes. Events resulting in brain insults during this period affect several neuronal elements that have far-reaching primary and secondary effects in terms of brain volume, and neuronal organization and function (Myers & Ment, 2009; Volpe, 2009; de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012).

Biological mechanisms

The brain lesions that infants born preterm have increased risk of are caused by inflammation and/or infection, and/or oxygen deprivation, and/or intracranial hemorrhages (Volpe, 2008). The infection/inflammation route
to brain lesions include maternal, placental, and infant infections/inflammations and the hypoxic/ischemic route involves the immature respiratory and vascular system of the infant born preterm. These events result in the activation of destructive mechanisms within the central nervous system. The activation of these mechanisms coincides with several maturational factors that interact and lead to brain injury (Burd, Balakrishnan, & Kannan, 2012; Ferriero & Miller, 2010; Volpe, 2009).

These destructive mechanisms (activation of microglia) are specifically detrimental to the immature oligodendrocyte, which later develop into myelin producing oligodendrocytes (Volpe, 2008, 2009). Other neuronal elements associated with the establishment of thalamo-cortical connections and proliferation of interneurons and glial cells have also been implicated (Bystron, Blakemore, & Rakic, 2008; Ferriero & Miller, 2010; McQuillen & Ferriero, 2005; Volpe, 2009). A sequela of microglial activation during the latter half of pregnancy has been shown to lead to reduced cerebral WM volumes (hypomyelination) due to the adverse effects on the immature oligodendrocyte (Volpe, 2008). Further, during the third trimester important organization of the cortex occurs when thalamic, association, and commissural projections enter the cortical plate. Synapses are formed and dendritic differentiation occurs. This is also a period of rapid development of the cerebellum (Volpe, 2009). The establishment of these neural connections (synapses) and the neural organization of the cortex have been shown to be important for many higher cognitive functions (Volpe, 2009).

Lesion types and their effect on brain development

The most frequently occurring insult in the infant born preterm is related to hypoxic-ischemic events and infection-inflammation. Far less common are intraventricular hemorrhagic infarction (IVH) and periventricular hemorrhagic infarction (Volpe, 2009). The most common lesion in the infant born preterm is periventricular leukomalacia (PVL) which is believed to be primarily caused by hypoxia-ischemia. PVL can also occur in the term infant with cardio-respiratory disturbance and in infants that have been exposed to maternal placental/fetal infection and inflammation (Volpe, 2008). PVL lesions have been shown to be present in 50% of preterm born infants with a birth weight of < 1500gram (Volpe, 2008) and in 80% of cases with CP, especially prominent in those with spastic diplegia (Johnston & Hoon, 2006). A systematic review of neuroimaging studies in CP has shown that 83% of individuals with CP have neuropathology, where WM abnormalities are the most frequently reported abnormality. The combination of WM and gray matter (GM) abnormalities is more common in persons with hemiplegic CP as this type of lesion usually occurs in fullterm births (Korzeniewski,
Birbeck, DeLano, Potchen, & Paneth, 2008). Hemiplegic CP is commonly caused by IVH (Nelson & Lynch, 2004) and intracranial hemorrhagic lesions occur in 25% of cases with PVL but are relatively rare in isolation (Volpe, 2008).

PVL has a focal and a diffuse component. In the focal component, all cellular elements are affected and the lesion can cause cyst and cavity formation in the periventricular WM or, more commonly, causes microscopic glial scars that are generally undetectable by neuroimaging. The diffuse component is more widespread in the WM and the immature oligodendrocytes are selectively affected (Volpe, 2008, 2009). The focal component is located in the deep WM at the end and border zones of the long penetrating arteries whilst the diffuse form is located in the area surrounding the short penetrators. One outcome of the diffuse form of PVL is hypomyelination which can be observed as an enlargement of the lateral ventricles as a result of the reduction of myelin (Volpe, 2008, 2009). Volpe (2009) suggests that the diffuse microscopic form of PVL may account for the cognitive and behavioral problems observed in preterm born children without major disability, whereas the macroscopic forms account for the motor deviations observed in cases with CP.

When the insult to the developing brain is severe, as often in IVH infarcts, similar effects on brain development to those described above are observed as part of the mechanism is the same. However, the site of hemorrhage is usually in close proximity to the descending corticospinal system (CS) and IVH usually destroys at least part of these fibers. The site of hemorrhage is also a region where neurons are proliferated, resulting in neuronal loss and migratory disturbance (Volpe, 2008). Much focus has been placed on the development of the CS system in relation to pre- and perinatal brain injury and CP. The CS system involves the corticospinal tract and the sensorimotor, premotor, and primary motor cortices from which it originates (Pitcher, Schneider, Drysdale, Ridding, & Owens, 2011). The CS system supports most skillful behaviors involving the forearm, hand and fingers. It is the last motor system to mature and its refinement is activity-dependent. It has been argued that the protracted activity dependency of CS system development makes it especially vulnerable to effects of pre-perinatal brain injuries. These lesions may sever the axonal connections between the brainstem and the cortex and as a result the CS system may be less able to establish synapses that lead to reduced hand function (Martin, 2005). These lesions to the CS system can lead to re-organization of motor control over the hands and arms to one hemisphere with retained and improved ipsilateral connectivity as observed in some individuals with hemiplegic CP (Staudt et al., 2002; Staudt, 2007).
However, in children born preterm with CP, the thalamo-cortical pathways have been shown to be more affected than the CS tract (Hoon et al., 2002, 2009). Further, a recent study in preterm born infants with no apparent cerebral lesions has shown that a reduced thalamic volume predicts a decreased cortical volume, lower volumes of the frontal and temporal lobes, including the hippocampus, and reduced integrity of the CS tract. These results were more prominent in lower GAs. The authors suggest that preterm birth has specific effect on the thalamo-cortical system that has secondary effects on related structures such as the CS system (Ball et al., 2012). These findings are in accordance with the vulnerable state of the neurons implicated in thalamo-cortical connectivity and the late migrating thalamic neurons during the latter half of pregnancy (Volpe, 2009). Taken together, these outcomes suggest that although motor impairments may be prominent (as seen in the studies by Hoon et al., 2002, 2009), the sensory system may be even more affected by WM lesions or developmental disruptions associated with a preterm birth. A sensory system that is readily implicated in WM lesions and disruptions in children born preterm is the cortical visual system. Specifically, the dorsal cortical visual stream which underpins visuo-spatial awareness, depth and motion perception has been implicated (Atkinson & Braddick, 2007; Taylor, Jakobson, Maurer, & Lewis, 2009). However, the involvement of the sensory systems does not exclude the importance of an intact CS system for sufficient upper-limb function but suggests more widespread effects on the brain than just the motor system. This is in accordance with the disruptions caused by microglial activation as previously described. Accordingly, a recent meta-analysis has shown comparable volumetric reductions of the whole brain, WM, GM, hippocampus, corpus callosum, and cerebellum in children born very preterm (< 33 GW) (de Kieviet et al., 2012).

Genetic factors

Both CP and preterm birth have been shown to be associated with genetic factors. In CP, several genetic mutations have been identified and the disorder has been shown to be heritable to some extent (Moreno-De-Luca, Ledbetter, & Martin, 2012). Costeff (2004) suggests that the brain lesions in CP are caused by genetics in about 40% of cases and by pre- and perinatal biological disturbances in 60% of cases. Further, it has been suggested that risk factors associated with CP, including a preterm birth, also have genetic underpinnings (Moreno-De-Luca et al., 2012). However, there are a limited number of studies that have investigated the genetics associated with a preterm birth but patterns of heritability and single gene mutations have been identified. For example, a twin study have shown that gestational length and birth weight are heritable to some extent (Clausson, Lichtenstein,
& Cnattingius, 2000). Risk factors associated with a preterm birth including inflammation, uterine contractions, and endocrines, to name a few, have been shown to have genetic underpinnings (reviewed in Behrman & Butler, 2007).

As explained, several maturational factors and their interaction with normally occurring developmental processes render the infant born preterm especially prone to the development of cerebral lesions and/or neuronal disturbances. These mechanisms do in some cases lead to the development of CP but may also be involved in adverse behavioral outcomes shown in children born preterm without diagnosed neurodevelopmental deviations (Ment et al., 2009; Williams et al., 2010; de Kieviet et al., 2009). Although it is likely that children born preterm and children with CP share much in terms of etiology, the limitations in motor functions and cognition differ. Hence, aspects related to the specific research questions regarding children born preterm will be described separately from those pertaining to the children with CP. Sensorimotor and intellectual function and hand-preference in children born preterm without major disability will be reviewed in the following section.

Sensorimotor and intellectual function in children born preterm

General motor functions and the relation to risk factors

Impaired motor and cognitive development have been stated to be the two major adverse sequelae of preterm birth (Pitcher et al., 2011). Indeed, studies have frequently shown that children with a preterm birth history without major disability have increased levels of motor impairment (Burns et al., 2009; Cooke, 2005; Davis, Ford, Anderson, & Doyle, 2007; De Kleine, Nijhuis-Van Der Sanden, & Lya Den Ouden, 2006; Edwards et al., 2011; Evensen, Skranes, Brubakk, & Vik, 2009; Foulder-Hughes & Cooke, 2003; Goyen & Lui, 2009; Hack et al., 2005; Holst, Grunau, & Whitfield, 2002; Jongmans, 1998; Leversen et al., 2011; Powls, Botting, Cooke, & Marlow, 1995; Rademaker, 2004; Schmidhauser, 2006; Skranes et al., 2008; Torrioli et al., 2000; Whitaker et al., 2006; Wocadlo & Rieger, 2008). A systematic review and meta-analysis of the literature reporting motor function outcomes in school-aged children born preterm without the diagnosis of CP showed a high prevalence of moderate (19/100) and mild-moderate (40.5/100) motor impairment (Williams et al., 2010). Likewise, a meta-analysis revealed significant and persistent general motor impairment in children born ≤ 32 GWs or with a BW ≤ 1500 gram without congenital
abnormalities. Fine motor skills were shown to be more affected than gross motor skills and of the subtests, balance and manual dexterity were shown to be most severely affected. The motor impairment was further shown to be greater in the preterm born children who had had perinatal complications than in those who had not (de Kieviet et al., 2009). Original research has shown that children born preterm have deficits in ball handling skills (Jongmans, 1998, also shown in the meta-analysis by de Kieviet et al., 2009) and handwriting (Feder et al., 2005). Further, a systematic review has shown that infants born preterm had a slower rate or lack of motor (Jongbloed-Pereboom, Janssen, Steenbergen, & Nijhuis-van der Sanden, 2012).

The motor problems observed in children born preterm without known neuropathology have been described as developmental coordination disorder (e.g. Foulard-Hughes & Cooke, 2003). A recent meta-analysis showed that 5-8 year old children born at < 33 GWs or with a BW of < 1500 grams that did not have CP were 6 times (odds ratio, OR = 6) more likely to fulfill the criteria for developmental coordination disorder than their fullterm peers. When the analysis was done applying a more generous criterion of developmental coordination disorder that included milder motor problems, the OR increased to 8.7 (Edwards et al., 2011). Recently, a compelling theoretical account for a continuum of impairment and shared causal pathways between developmental coordination disorder and CP has been postulated (Pearsall-Jones, Piek, & Levy, 2010). The idea of shared causal mechanisms is appealing from a biological perspective as the lesions observed in CP are usually the most profound, although with a wide range in severity, with severe effect on sensorimotor function. It is plausible that less severe lesions and/or disruptions in brain development may cause less severe but persistent sensorimotor impairments in children born preterm without major disability.

Other research groups have described the deviations observed in children born preterm without major disability as minor neuromotor dysfunction. Children with minor neuromotor dysfunction display neuromotor abnormalities that are persistent but show only mild to moderate impairment in motor function and may have mildly delayed motor development (Behrman & Butler, 2007). Mild minor neuromotor dysfunction has been shown to be highly prevalent in children born preterm (44% in children born < 33 GWs and 31% in children born at 33 to 34 GW) at 5 years of age. Further, the presence of mild or minor neuromotor dysfunction in children born very preterm (< 33 GWs) was shown to be associated with cognitive impairment, learning difficulties, and behavioral and emotional problems (Arnaud et al., 2007).
Efforts have also been made to identify specific factors that affect motor functions. In a study where 8 year old children born preterm (< 29 GWs or with a BW < 1000 grams), whereof 42% were classed as having motor impairments, retinopathy of prematurity (ROP; abnormal vascularization of the retina which may result in loss of vision and problems with acuity), and prolonged rupture of membranes were independently associated with poorer motor outcomes. Importantly, the children born preterm included in the study all attended mainstream school, were free of disability, had no neurological impairment or visual or hearing deficits, and had a full scale intelligence quotient (IQ) of > 84 points (Goyen & Lui, 2009). Other studies have shown associations between poor motor function and the degree of neurological impairment (Schmidhauser, 2006), presence of cerebral insult in the neonatal period (Davis et al., 2007; Schmidhauser, 2006; Whitaker et al., 2006), lower GWs (Cooke, 2005; Foulder-Hughes & Cooke, 2003; Leversen et al., 2011), lower BWs (Foulder-Hughes & Cooke, 2003), being small for gestational age (SGA) (Leversen et al., 2011), male sex (Davis et al., 2007; Leversen et al., 2011; Whitaker et al., 2006), female sex (Powls et al., 1995), number of days in ventilation in the neonatal period (Whitaker et al., 2006), lower general IQ (Foulder-Hughes & Cooke, 2003), problems with literacy and/or numeracy (Wocadlo & Rieger, 2008), poor academic achievement, behavioral problems, externalizing behaviors (Davis et al., 2007), visual impairment (Evensen et al., 2009), diagnosis of ROP (Leversen et al., 2011), and poor physical fitness (Burns et al., 2009). Further, a recent meta-analysis showed that visuo-motor integration was negatively affected in children born < 33 GWs or with a BW of < 1,500 grams. The impairment in visuo-motor integration was worse for the children with male sex, low IQ, and lower GAs (Geldof, van Wassenaer, de Kieviet, Kok, & Oosterlaan, 2012).

**Intellectual function in children born preterm**

Several studies have reported lower scores, albeit in the normal range, on tests measuring cognition in children born preterm (e.g., Allin et al., 2001, 2011; Bhutta, 2002; Foulder-Hughes & Cooke, 2003; Kontis et al., 2009). In the meta-analysis by Bhutta and colleagues (2002), the cognitive test scores were directly related to GA and BW, where the children with the lowest GAs and BWs had the lowest cognitive test scores. This finding is most likely related to the increased level of physiological immaturity of the infant born at very (28-32 GWs) or with extremely (< 28 GWs) low GAs and BWs as the risk of neurological insults increases with decreasing GA and BW. Other studies have not been able to show an association between GA and IQ, possibly due to the small number of children born extremely preterm in the study samples (Bos & Roze, 2011). Very preterm (< 33 GWs) born adolescents with or without neonatal brain lesions that had comparable GAs
have been shown to have lower IQ than those born fullterm. Further, those with neonatal brain lesions had significantly lower IQ scores than the children born preterm without cerebral lesions and the children born fullterm, respectively. It was also shown that IQ scores correlated with volumes of the WM and corpus callosum and that these volumes explained 70% of the variance in IQ within the preterm born groups (lesion/no lesion). The IQ scores also correlated positively with academic achievement in the children born preterm (Northam, Liégeois, Chong, Wyatt, & Baldeweg, 2011). However, other studies have not been able to show a connection between brain lesions and cognitive outcome in children born preterm, again possibly due to small study samples (Bos & Roze, 2011). Other factors associated with adverse cognitive development in children born preterm have been identified. These factors include late-onset sepsis (van der Ree, Tanis, Van Braeckel, Bos, & Roze, 2011), GA, patent ductus arteriosus, head circumference at the age of 7 (Cooke, 2005), male sex, number of ventilation days and white matter injury as detected by neonatal ultrasound (Whitaker et al., 2006). Where standardized IQ tests have been used, a global lowering of intellectual function is usually reported (e.g., Allin et al., 2001, 2011; Hoff Esbjørn, Hansen, Greisen, & Mortensen, 2006; Kontis et al., 2009; Peterson et al., 2003; Soria-Pastor et al., 2009).

There is a general consensus that intellectual abilities are underpinned by higher cognitive or executive functions and processes. Studies aimed at investigating the executive functions in children born preterm have shown substantial impairments compared to children born fullterm (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012; Mulder, Pitchford, Hagger, & Marlow, 2009; Mulder, Pitchford, & Marlow, 2010). Observed deficits in executive function in children born very preterm include verbal fluency, cognitive flexibility, response inhibition, planning, and verbal and spatial working memory (Aarnoudse-Moens et al., 2012; Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009). Further, performance on tasks tapping executive function in children born preterm has been shown to be negatively influenced by a history of ROP and current visual impairment (Böhm, Smedler, & Forssberg, 2004) suggesting functional interrelatedness. Despite an early visual advantage in infancy (Hunnius, Geuze, & Zweens, 2008; Ricci et al., 2008), children born preterm have readily been shown to have lower test scores than fullterm born controls on tasks with high demands on visual function (e.g., Geldof et al., 2012; Hoff Esbjørn et al., 2006). The visual deficits or delays shown are not exclusively related to the functions of the eye but also to the function of cortical visual systems. Children born preterm with PVL have readily shown cortical visual impairment (Weinstein et al., 2012). Specifically, children and infants born preterm have been shown to have visual deficits supported by
the functions of the dorsal visual stream, the where and how visual system (Atkinson & Braddick, 2007; Weinstein et al., 2012). The dorsal stream is involved in the processing of motion, spatial awareness, and depth perception. It originates in the occipital lobe and terminates in the posterior parietal cortex. It is a cortical visual system that provides a 'coordination system' of the visual environment whereon our movements are organized. The intactness of the dorsal visual stream is important for accurate motion in three dimensional space and dysfunction of it can be manifested in clumsiness and compensatory movements in order to improve end point accuracy (Dutton, 2003). Thus, the dorsal cortical stream is an important part of a visuo-motor system that is highly involved in the transformation of visual information into action. In addition, poor visuo-motor performance has been associated with poorer executive functions, specifically inattention and hyperactivity in children born preterm (Böhm, Lundequist, & Smedler, 2010).

Relations between motor function and cognition in children born preterm

Historically, cognitive and motor development has generally been regarded as separate entities with largely independent developmental trajectories and neurological underpinnings (Davis, Pitchford, & Limback, 2011). However, this view is beginning to be increasingly challenged by findings of interrelated cognitive and motor functions in both healthy and at-risk children. Cognition and motor performance, specifically visual perception and fine motor control have been shown to be highly interrelated in typically developing children (Davis et al., 2011). A recent study has also shown strong correlations between the volumes of the cortical GM, caudate, and cerebellum and cognition in fullterm born typically developing children, suggesting the importance of specific structures in cognitive functions. However, although fine motor skill was strongly correlated to cognitive outcomes, no correlation between brain volumes and motor performance was found. These findings may reflect the dispersed neural networks supporting motor functions and also implicating cognitive functions as an important mediator of motor performance (Pangelinan et al., 2011).

Relatively few studies have focused on the investigation of the associations between cognitive outcomes and motor function in prematurely born populations. However, there is a growing body of evidence associating a lower level of intellectual ability with motor skill impairments within groups of children born preterm. Foulder-Hughes and Cooke (2003) found significantly lower scores on the Wechsler’s Intelligence Scale for Children, III edition in children born < 32 GWs compared to typically developing
children born at term. The cognitive outcomes were negatively correlated to
motor outcome measures. Similarly, connections between academic
underachievement and poor motor function have been shown in children
born preterm (< 30 GWs) where increasing severity of motor impairment
corresponded to higher degree of underachievement (Wocadlo & Rieger,
2008). Further, poorer motor skills, in particular fine motor skills, have been
associated to the occurrence of sepsis in children born preterm (van der Ree
et al., 2011). A recent meta-analysis showed deviations in visuo-motor
integration in children born preterm. Visuo-motor integration is reliant on
visuo-spatial ability, fine motor abilities, and motor planning. The results
from the meta-analysis showed that GA, male sex, and full scale IQ were
associated with visuo-motor integration outcome where lower GAs, boys,
and lower IQ were connected to poorer visuo-motor functioning (Geldof et
al., 2012). Further, evidence is emerging that connect the function of the
motor cortices to higher cognitive processing including auditory and visual
speech perception and comprehension (Pitcher et al., 2011). Thus, the study
of the connections between motor function and cognition in preterm born
children is an important area of research.

**Upper-limb goal-directed movements in children born preterm**

As has been reviewed in the text above, there is evidence that children born
preterm have higher levels of motor impairments, specifically prominent in
balance, manual dexterity and visou-motor function (Atkinson & Braddick
2007; Feder et al., 2005; Jongmans, 1998; Schmidhauser, 2006; de Kieviet
et al., 2009). Given the effect a preterm birth can infer on the development
of the CS and visual systems such deviations are plausible. The WM integrity
of the motor region (CS tract) has been shown to be related more to motor
skills than GA in healthy neurologically intact 11 year-old-children born
between GW 24-41 (see Pitcher et al., 2011). Reaching, grasping and
prehensile movements have been argued to be the most fundamental of
manual skills. Such movements place high demands on control over
shoulder, elbow, wrist and finger joints as well as posture and balance
(Michel, 1991). In the study by Schmidhauser (2006), fine motor skills were
shown to be particularly impaired in children born preterm. A handful of
studies exist that have focused primarily on the kinematics of reaching (and
grasping) like movements in infants (Fallang, Saugstad, Grøgaard, &
Hadders-Algra, 2003; Grönqvist, Strand Brodd, & von Hofsten, 2011; Toledo
& Tudella, 2008) and children born prematurely (Sagnol, Debillon, & Debû,
2007), often from a perspective of early identification of neuromotor
deviations. Less optimal reaching and catching has been shown in 8-month-
old infants born very preterm as expressed by a bimanual catching strategy
and less energy-efficient movement paths (Grönqvist et al., 2011). Similarly,
less optimal reaching behavior in infants born preterm deemed to have a high risk of neurodevelopmental deviation was evident at 6 months corrected age (Fallang et al., 2003). In a follow up study of the same infants at 6 years of age the inability to successfully reach and grasp at 4 months and less optimal reaching and grasping at 6 months of age was related to a complex form of neuromotor dysfunction at school age. Further, problems with postural control in infancy were associated with a simpler form of minor neurological dysfunction at 6 years of age (Fallang et al., 2005). Visuo-motor control, in terms of error rates, movement segmentation, and movement duration, have also been shown to be negatively affected by a very preterm birth in 3.5 and 5 year old children (Sagnol et al., 2007).

**Handedness and movement performance in children born preterm**

An important aspect of manual control is hand dominance where studies have shown that the preferred hand manipulates objects and the non-preferred hand acts as a stabilizer (MacNeilage, 1987). If the action is bimanual with equal force constraints for both hands, the preferred and non-preferred hand are used interchangeably as the acting hand depends on the spatial location of the goal (Johansson et al., 2006). The expression of handedness is the most striking observable form of human asymmetry and its establishment is affected by genetic factors, environmental effects and experiences during development, asymmetries in neurochemistry, and disease (Toga & Thompson, 2003).

The origins of handedness is a long debated issue (see Hopkins & Rönnqvist, 1998 for a comprehensive theoretical account). A right sided preference for the hand, foot, eye, and ear are usually found in the normally developing population. About 90% of the population has been reported to have a right hand preference (Porac & Coren, 1981). Although there is no question about the dominance of a right-hand preference in the general population, lower rates of right handedness have been reported (≈ 80%) (McManus, Rawles, Moore, & Freegard, 2010). Further, males have been reported to have higher frequencies of a non-right hand preference than females (e.g., Nicholls, Johnston, & Shields, 2012). It is possible that the somewhat diverging results from studies that report rates of hand preference could be a result of differing assessment methods and population biases. Handedness has been shown to be heritable, at least to some extent, and theories have been developed based on genetic heritance principles (Annett, 1985). The right shift theory suggests that the absence or presence of a single gene that codes for cerebral asymmetry, primarily of language which usually is located in the left hemisphere, increases or decreases the probability of subsequent right
handedness. Others have described all non-right handedness as having a pathological origin stemming from pre- or perinatal neurological insult (Bakan, 1971; Bakan, Dibb, & Reed, 1973). Further, the risk of birth stress and thus a non-right hand preference has been suggested to be heritable (Bakan, Dibb, & Reed, 1973). In these theories one does not inherit a hand preference per se but the risk of birth stress that in turn cause a non right hand preference. Other models suggests that there might be both heritable natural and pathological origins of non-right handedness where early neurological lesions constitute the pathological type in at risk populations, such as premature birth (Bishop, 1990; Satz, 1972; Soper & Satz, 1984). The occurrence of non-right handedness or less strong hand preference has been implicated in a number of developmental disorders, often with genetic associations, (e.g., Hauck & Dewey, 2001) and in children with prenatal exposure to teratogens (Domellöf, Rönnqvist, Titran, Esseily, & Fagard, 2009). Handedness is regarded as a reflection of the asymmetric organization of the sensorimotor system and the expression of a non-right hand preference may be a sign of disruption in the organization of the brain (Sacco, Moutard & Fagard, 2006).

Although it has been suggested that motor performance and handedness are different entities, studies have shown that motor performance is better with the preferred hand in both right and left handers (Triggs et al., 2000; Triggs, Calvanio, & Levine, 1997). Similarly, it has been shown that the distal muscular control in the preferred hand is more refined than in the non-preferred and that when using the non-preferred hand for a task demanding highly skilled actions (handwriting) more proximal musculature is used (Mack, Rothi, & Heilman, 1993). However, it was shown in the study by Triggs and colleagues (2000), by use of regression analysis, that 90% of left-handers and 93% of right-handers were categorized into the correct handedness classification based on scores from motor performance tests (finger tapping and pegboard) showing a less than perfect relationship between performance and hand preference.

It is possible that the events associated with a preterm birth may affect the development of brain organization through neuropathological and environmental influences. To exemplify, an effect of such events on side specificity may be seen in hemiplegic CP, where hemorrhage in primarily one cerebral hemisphere results in extreme side specificity. There are some studies that have investigated the occurrence of non-right handedness in children born preterm (Marlow, Roberts, & Cooke, 1989; O’Callaghan, Burn, Mohay, Rogers, & Tudehope, 1993; Powls et al., 1995; Ross, Lipper, & Auld, 1987, 1992; Saigal, Rosenbaum, Szatmari, & Hoult, 1992) showing a slight increase in left and non-right handedness. However, few studies have related
Cerebral Palsy

Functional impairments in children with CP

CP is the most common developmental disturbance causing lifelong physical disability (Aisen et al., 2011; Krägeloh-Mann & Cans, 2009). The most recent internationally accepted definition of CP reads:

“Cerebral palsy (CP) 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 behaviour, by epilepsy, and by secondary musculoskeletal problems.”

(Rosenbaum, Paneth, Leviton, Goldstein, & Bax, 2008, p. 9)

The motor problems associated with CP form the basis for diagnosis of the syndrome although severe sensory and cognitive deficits are common (Cans, 2007; Straub & Obrzut, 2009). Children with CP have deficiencies in the control of muscle tone where it is either too high (hypertonia) or too low (hypotonia) or a combination of the two. CP can be classified into three types with different profiles of motor deviations. The first subtype is spastic CP where at least two of the following symptoms must be present: Increased
tone, pathological reflexes, and an abnormal pattern of movement and/or posture. The spasticity may be located to limbs on both sides of the body (bilateral spastic CP) or one side (spastic unilateral CP) (Cans, 2007). The unilateral subtype (hemiplegic CP) is the most commonly occurring subtype accounting for 38% and the bilateral (diplegic CP/tetraplegic CP) form has a prevalence of 39% (Himmelmann et al., 2010). The second type is ataxic CP which is characterized by abnormal posture and/or movements and by movements that are uncoordinated with too high or low force, abnormal rhythm, and decreased accuracy (Cans, 2007). This is the rarest form, present in 5% of cases with CP (Himmelmann et al., 2010). The third type is dyskinetic CP where the motor profile contains movements that are involuntary, uncontrolled, sometimes stereotyped, and recurring. Dyskinetic CP may be dystonic, where movements are hypokinetic (stiff movements, reduced activity) and hypertonic (unusually high tone) or choreo-atheotic, where movements are hyperkinetic (stormy movements, increased activity) with hypotonicity (unusually decreased tone). Dyskinetic CP has been shown to be present in 17% of cases with CP (Himmelmann et al., 2010).

In a study by Himmelmann and colleagues (2006), the majority of children with CP were shown to have mild to moderate gross (70%) and fine (75%) motor impairments; a minority were thus shown to have severe limitations (gross motor function -30%; fine motor function -25%). The severity of gross motor impairment was further shown to increase as GA decreased. The limitations in gross and fine motor function differed between the different types of CP. Most (95%) of the children with spastic hemiplegic CP have mild/moderate (Gross Motor Function Classification System; GMFCS; level I-II) gross motor impairment and those with spastic diplegic CP were found to have both mild/moderate (54%) and severe (GMFCS IV-V) (31%) gross motor impairment. Most of the children with spastic tetraplegia (100%) and dyskinetic CP (96%) had severe gross motor impairments whereas most of the children with ataxia had mild/moderate impairments. In general, the manual ability corresponded to that of the gross motor performance. The same study showed high rates of learning disability (40%), epilepsy (33%), and severe visual impairment (19%). Further, the number of accompanying impairments also increased with the level of gross motor function. Children with ataxia and hemiplegic CP had the lowest rates of accompanying impairments and milder learning disability. Accompanying impairments were most prevalent in tetraplegia and in those children born < 28 GWs (Himmelmann, Beckung, Hagberg, & Uvebrant, 2006). It is apparent that children with CP have functional difficulties in numerous domains. A literature review has shown that; visuo-perceptual problems are highly prevalent, verbal function is usually higher than non-verbal function (at least for the less severe cases), learning problems occur in about half of the
children with CP, short-term memory is problematic, and that executive functions are negatively affected (Straub & Obrzut, 2009).

**Risk factors for the development of CP**

Being born preterm is the single most important risk factor for later development of CP and half of those diagnosed with CP have been born prematurely (Beaino et al., 2010). Several different risk factors for the development of CP have been identified. Being born before GW 28 has been shown to be the single most important risk factor in one study (Sukhov, Wu, Xing, Smith, & Gilbert, 2012) and for children born ≤ 32 GWs the presence of cerebral lesions has been shown to be the best predictor (Beaino et al., 2010). Other significant contributions to the development of CP are birth asphyxia, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage (Sukhov et al., 2012), male sex, preterm premature rupture of membranes, spontaneous onset of labor before rupture of membranes (Beaino et al., 2010), and genetic factors (Moreno-De-Luca et al., 2012). Birth defects have been associated to increased risk of CP in both preterm born and term born children (Sukhov et al., 2012). In preterm born children, the risk of developing CP has been shown to increase with the number of pre- and perinatal risk factors (Stoknes et al., 2012; Sukhov et al., 2012). Of preterm born children with CP, 9% have been shown to have preterm birth as a single risk factor (Stoknes et al., 2012).

**Brain lesions in CP**

70-80% of the lesions causing CP can be related to insults occurring prenatally (Moreno-De-Luca et al., 2012). In a population-based study by Himmelmann and colleagues (2010), it was found that 36% of lesions in children with CP could be attributed to prenatal insults and 42% to the perinatal period whereas 21% remained unclassifiable. However, it is difficult to determine the timing of the insult depending on the clinical expression of CP as different etiologies at different times in development can result in the same clinical expression and vice versa (Korzeniewski et al., 2008). Further, the preciseness of the dating of lesions in CP imaging outcomes has also been questioned as migrational processes have been shown to carry on later on in early brain development than previously thought (Hüppi et al., 1998; Lenroot & Giedd, 2006). With this in mind, there are indications that insults in the first or early second trimester cause malformations due to disturbances in migration processes (Krägeloh-Mann et al., 1995). Malformations are more common in term infants and more prominently found in hemiplegic CP than other types. Malformations have been found to be prevalent in 10% of cases with CP (Korzeniewski et al., 2008). During the
latter parts of the second trimester and the third trimester, cerebral WM insults (PVL) are prominent and occur primarily in the preterm born infant. When there is WM injury in isolation, the result is often bilateral spasticity, atheosis and ataxia. WM insult is the most common finding in CP (83%) (Korzeniewski et al., 2008). PVL is also relatively common in fullterm born infants although the distribution is then bilateral cortical-subcortical (Johnston & Hoon, 2006). When the events leading to PVL are accompanied by hemorrhages, the infarct is often unilateral and results in hemiplegic CP (Candy, Hoon, Capute, & Bryan, 1993; Cioni et al., 1999). When insults occur in the latter part of the third trimester, cortical and subcortical GM and the periventricular WM are primarily affected (Candy et al., 1993; Korzeniewski et al., 2008; Krägeloh-Mann et al., 1995). Absence of detectable adverse neuroradiological findings has been reported in 17% of cases with CP, (Korzeniewski et al., 2008).

**Goal-directed upper-limb movements in CP**

Several studies have investigated upper-limb function in children with CP with focus on movement organization, control and planning. To study the central aspects of the sensorimotor deviances in CP is of importance. Motor planning impairment in CP has been argued to be just as disabling as the functional impairments deriving from biomechanical constraints (Steenbergen & Gordon, 2006). Studies have shown deficits in the planning and timing of movements in hemiplegic CP where reaching trajectories have been shown to more often consist of more than one movement segmentation, have longer durations, and involve more proximal control (Butler, Ladd, Louie, et al., 2010; Butler, Ladd, Lamont, & Rose, 2010; Coluccini, Maini, Martelloni, Sgandurra, & Cioni, 2007; Domellöf, Rösblad, & Rönqvist, 2009; Hung et al., 2012; Jaspers et al., 2011; Kreulen, Smeulders, Veeger, & Hage, 2007; Mackey, Walt, & Stott, 2006; Ricken, Savelsbergh, & Bennett, 2006; Rönqvist & Rösblad, 2007; Steenbergen, Thiel, Hulstijn, & Meulenbroek, 2000; van der Heide, Fock, Otten, Stremmelaar, & Hadders-Algra, 2006). These results have been interpreted to reflect compensatory behavior in order to increase end-state control. Kinematic analyses have also shown that the less-affected upper-limb in hemiplegic CP has deviations in terms of increased postural involvement (Domellöf, Rösblad, et al., 2009; Hung et al., 2012; Steenbergen & Meulenbroek, 2006), longer movement durations, and later peak amplitudes (Hung et al., 2012). Despite these studies and the importance of the arms and hands in daily living, relatively little is known about the nature of the deficits in goal-directed upper-body movements in CP. Increased knowledge regarding these impairments could prove important in the development of suitable intervention methods for this population.
The malleable brain

Plastic changes in development

Plasticity pertain to the altering of the functional organization of the brain in response to experience, learning, and recovery from injury (Holt & Mikati, 2011; Johnston, 2009; Nudo, 2006). Plasticity processes have been studied in children who have unilateral pre-perinatal brain injury in attempts to understand how cortical organization processes are affected by such events (Staudt, 2007, 2010) and to inform rehabilitative practice (Nudo, 2006). The immature brain has greater vulnerability to brain insults (Volpe, 2009) and at the same time increasing ability for neural plasticity (Staudt, 2007). Early occurring insults may result in the reorganization of a function (i.e. language being established in the contra-lesional right hemisphere) or the maintenance and refinement of ipsilateral CS projections to the hand affected by the insult (contralesional). Afferent aspects of language and motor function (somatosensory processing and speech perception) have been shown to remain in the lesioned hemisphere (Staudt, 2007). In hand function, the ipsilateral connections have been shown to be functional in fullterm and preterm born infants where trans-magnetic stimulation has been shown to evoke bilateral activity in the upper limbs, with faster latencies in the ipsilateral hemisphere (Eyre, Taylor, Villagra, Smith, & Miller, 2001). The ipsilateral advantage was reduced during the first two years of development whereas the contralateral projections became more established. In infants with unilateral brain lesions, there was no down-regulation of the function of the ipsilateral connections (Eyre et al., 2001). These findings suggest activity dependence in the formation of the motor system supporting manual dexterity (Eyre et al., 2001; Martin, 2005) and the maintenance and establishment of ipsilateral connections should be regarded as a sign of disturbance of developmental processes and not a reparative function of the central nervous system (Eyre, 2007).

Plasticity and interventions

There has recently been a shift in the approach to the management of CP, deriving from knowledge generated in the research field of neuronal plasticity, where the central rather than the biomechanical impairments are addressed (Schertz & Gordon, 2009; Wittenberg, 2009). Effects of early interventions have been studied in preterm born infants. A meta-analysis using studies with case-control design revealed that intervention programs aimed at children born preterm that involve occupational therapy, physical therapy, and neuro-psychological methods improved cognitive performance in the short term (infancy and preschool ages) but no effect was observed on
motor function (Spittle, Orton, Doyle, & Boyd, 2007). Similar results were presented by the same authors when only including randomized controlled studies (Orton, Spittle, Doyle, Anderson, & Boyd, 2009). The results from these meta-analyses might have been different if the sample had been stratified by GA and/or presence of brain injury. A systematic review has shown that increased brain growth and improved cognitive functions have been shown to be the result of diets high in protein and exposure to rich environments in infants with perinatal brain injury (Holt & Mikati, 2011).

In CP, most intervention methods are applied when the diagnosis is set, which is usually late in terms of brain development. However, activity-dependent plasticity appears across the lifespan, making therapies aimed at improving function in older children and adults with CP feasible (Wittenberg, 2009). Mechanisms behind activity-dependent plasticity not only relate to the establishment and refinement of ipsilateral projections but also to motor cortical organization. Studies of primarily monkeys have shown that repeated activation alone is not sufficient to induce longstanding and large functional changes. Such changes appear to be established by movements with increasing demands on motor skills that involve multiple joints in complex movement repertoires. Training such skills generates motor cortical representations of multiple joint modules that, when established, result in automatic co-activation of the joints represented in the movement and the experience of a temporally timed execution. Further, plasticity is best induced if feedback is given on performance and if the degree of difficulty gradually increases (Nudo, 2006).

There is evidence supporting activity-based plasticity in hemiplegic CP in response to constraint-induced movement therapy methods, with relatively large and sustained improvements where the affected arm and hand are used more frequently after the intervention (Huang, Fetters, Hale, & McBride, 2009). Further, action planning in terms of end-state comfort has been shown to be positively affected after 8 weeks of intensive bimanual training combined with constraint induced movement therapy in 3-6 year old children with hemiplegic CP (Crajé, Aarts, Nijhuis-van der Sanden, & Steenbergen, 2010).
OBJECTIVES

The main objectives of this thesis were to investigate sensorimotor behaviors in children born preterm and in adolescents with CP. Hand preference, side specific movement performance, and intellectual functioning are aspects that have been shown to be affected by a preterm birth but few studies have explored the relation between these. Studies I, II, and III are therefore focused on the investigation of these aspects in children born prematurely, without major disability, by employing both meta-analytical, frequency based assessments, and kinematic movement analyses. Further, persons with CP have a longstanding need of intervention methods that are aimed at maintaining and improving functional capacity. Thus, investigations into the effects of a sensorimotor training method on upper-body movement performance in adolescents with CP were an important objective (study IV).

The following questions were posed:

*Does a preterm birth affect the functional organization of the motor system as expressed by increased rates of non-right handedness?*

*Do children born preterm without major disability have less well organized upper-body movements during a goal-directed task with high demands on precision compared to fullterm born children? Does GA affect these outcomes?*

*Do children born preterm and their fullterm born peers express side specialization in terms of more effective and well organized movements with their preferred hand? Does GA influence the outcomes?*

*Is upper-body movement organization in fullterm born children associated with intellectual function when controlling for the effects of GA and sex?*

*Does synchronized metronome training improve upper-body movement organization, both in the short and long term, in adolescents with cerebral palsy and will such changes have effect on activities in daily life?*
METHODS

A number of different study designs, statistical methods, and assessment methods are used in the studies in this thesis. In the following section the details of the studies from a methodological perspective will be given, starting with study design followed by descriptions of the participants and how they were recruited, a detailed description of the assessment methods including procedures, the statistical methods applied, and ethical considerations. To improve associability of the text for the reader, the methods related to the systematic review and meta-analysis (study I) will be described first in a separate section, followed by a section with the methods related to the empirical studies (studies II-IV).

Systematic review and meta-analysis (study I)

Study design and inclusion criteria

To explore the frequency of non-right handedness and its relation to neurological and neuropsychological functions in children born preterm, a meta-analysis and systematic literature review was performed. Suitable peer-reviewed English language papers reporting hand dominance in children born preterm were located by searching eight electronic databases using a combination of the search terms "preterm", "prematurity", "premature", "low birth weight" and "handedness", "hand preference", and "hand dominance" and "children". The reference lists of the included publications were also searched manually. The inclusion criteria stated that the children born preterm had to be born < 37 GWs and be between 3-18 years of age, and the studies had to be of case-control design, where the participants were comparable with regard to age and sex. The studies had to be published in the 30 year period between September 1980 and September 2010. When multiple publications derived from the same research team, efforts were made to eliminate overlapping samples by contacting the authors of the papers. Further, to maximize the number of cases included in the meta-analysis, authors were contacted when sample integrity was unclear with regard to GAs. Then unpublished data (participants included in studies II and III) was also included in an attempt to combat the "file drawer problem".

Quality assessment

Independent quality assessments were made by two of the authors where the included studies were rated on aspects of the characteristics of the study population, comparability of cases and controls, representativeness of the
cases to the untested cases in the cohorts, the methodology applied in testing handedness, and the relation between handedness and other outcomes. One important reason for assessing the quality of the included studies was to test whether sample heterogeneity was due to differing study characteristics. Further, we assumed that studies with well described study samples and more rigorous study designs would yield results where group differences were more readily detected and thus results that were more accountable.

**Statistical methods**

The statistical analyses in study I was carried out in Comprehensive Meta-Analysis 2.2 (BioStat Inc., Englewood, NJ, USA). As the samples were shown to be heterogeneous an odds-ratio meta-analysis was chosen to investigate the occurrence of non-right handedness in the prematurely and fullterm born children. The confidence interval was set at 95% and the alpha value at 0.05. As meta-analyses by nature involve study samples recruited from different populations that are assessed by means of different methods, statistical homogeneity was assessed. Statistical homogeneity refers to the approximated variance in study outcomes (point estimates) among studies that are due to differences in study samples and methods and not chance (Higgins, 2008). The homogeneity in the included studies was statistically assessed using the \( I^2 \) method, where \( I^2 = [(Q - df)/Q] \times 100\% \) (\( Q = \) chi-squared statistic, \( df = \) degrees of freedom), which results in a percentage measure of the approximated heterogeneity. A heterogeneity value of < 40% may be unimportant, 30-60% may reflect a moderate level, 50-90% may be interpreted as a substantial level, and 75-100% may indicate a considerable level. The magnitude of the heterogeneity was assessed by use of \( \tau^2 \) (tau squared) statistics, which provides a point estimate of the amount of variance across studies that is calculated on the actual effects (Higgins, Thompson, & Spiegelhalter, 2009). Sources of heterogeneity should, if possible, be investigated as results may otherwise be over-interpreted (Thompson, 1994). Hence, the quality assessment scores were used as sensitivity measures as they refer to some of the factors assumed to have effect on among study variance.

As there in general is a risk that non-significant results are omitted from publication, the so called "file drawer problem", it is important to perform analyses that investigate the risk of publication bias. In the present study, the risk of publication bias should be limited as only six of the included studies had handedness as a principal research question (Ashton, 1982; Ehrlichman, Zoccolotti, & Owen, 1982; O'Callaghan et al., 1993; Powls, Botting, Cooke, & Marlow, 1996; Ross et al., 1987; Saigal et al., 1992), few of the other studies tested handedness differences between study groups.
statistically, and unpublished results were included (Rönnqvist et al., unpublished results). The occurrence of publication bias was assessed by visual inspection of funnel plots where the standard error was plotted as a function of study OR. Studies with large sample sizes will cluster close to the combined point estimate near the top of the inverted funnel and studies with smaller sample sizes will cluster closer to the bottom of the inverted funnel with wider spread from the combined point estimate. If there are discrepancies in which side of the combined point estimate the studies with small samples occur, there may be publication bias in the dataset. If no publication bias exists, the inverted funnel will be symmetrical (Higgins & Green, 2011; Sterne & Egger, 2001). The tendency of smaller sample studies to cluster on one side of the combined point estimate has also been termed the "small study effect" (Sterne & Egger, 2001; Sterne, Gavaghan, & Egger, 2000), which is the tendency of smaller studies to show larger treatment effects and to be omitted from publication if they show null effects to a greater extent than studies with large sample sizes (Higgins & Green, 2011; Littell, Corcoran, & Pillai, 2008). The occurrence of an apparent "small study" effect may also indicate variations in the methods applied, differing clinical samples, and heterogeneity effects thus caution is warranted when investigating the funnel plot. Likewise, a non-significant result on tests of publication bias does not guarantee that publication bias is non-existent (Higgins & Green, 2011). In the present study, Egger's test of the intercept, which is a linear regression model that tests for the "small study" effect, was used when statistically testing publication bias (Egger, Davey Smith, Schneider, & Minder, 1997). An inverse correlation is expected between effect size and study size. The bias is quantified by regressing the standardized effect on the inverse standard error. The slope is the size of the treatment effect and the intercept and its significance level indicates publication bias (Egger et al., 1997). Sensitivity analyses of the extent of publication bias were conducted by means of Duval and Tweedie’s trim-and-fill method (Duval & Tweedie, 2000; Littell et al., 2008). This method rests on the assumption that point estimates of individual studies should appear symmetrically around the combined point estimate in the funnel plot. If the plot is asymmetrical, a number of studies are imputed to create an apparently symmetrical plot and as a result of this the combined point estimate is trimmed (Duval & Tweedie, 2000). If the asymmetry in the plot is caused by the “small study” effect, the imputed studies will appear at the bottom of the funnel plot (Littell et al., 2008).
Empirical studies (studies II-IV)

Study designs

Handedness, movement performance, and intellectual function in children born preterm (studies II and III)

To assess handedness, movement performance in general and with the preferred and non-preferred hand, and intellectual function in children born preterm, a case-control study was performed. The study design enabled comparison of the children born preterm with a group of fullterm born children who were similar in age and sex. The groups involved children of 4 to 8 years of age and thus important information about age related changes of the included children could be obtained. The assessment battery was piloted on a number of typically developing children before the study commenced.

Short- and long-term effects of timing and rhythmicity training on upper-limb movements in children with cerebral palsy (study IV)

In study IV, the effects of the SMT method, the Interactive Metronome (IM), on goal-directed upper-body movements in adolescents with differing severity of CP were explored. Before the individually adjusted IM training commenced, the participants completed a pre-test battery that included kinematic movement registrations, measures of timing and rhythmic ability, gross motor function and hand function. When the IM training had been completed, a post-test battery was applied, where movement kinematics, timing and rhythmic ability, and the subjective experience of possible training effects were assessed. This battery was applied twice, immediately after training completion (Post-test 1) and 6 months after training completion (Post-test 2). The kinematic task was piloted on a typically developing 13 year old child before the study was instigated. The study design is summarized in figure 1.
Individually adjusted IM training 12 sessions x 30 min

Timing/rhythmic assessment (IM)*
Kinematic movement registration
Questionnaire
* Assessed at every training occasion

Figure 1: Schematic illustration of the study design and the included assessments at each time point.

**Participant description and recruitment process (study II-IV)**

**Studies II-III**

Sixty-eight children born at < 35 GWs and cared for at the neonatal intensive care unit at Norrland’s University Hospital, Umeå, Sweden between January 2000- June 2003 and January 2004- June 2005 were recruited. 376 children were identified from the birth records, where 225 could be localized through the civil register. Of the initial 376, some could not be located, had moved abroad or were deceased. Of the 225 that were located, 126 were selected for invitation to the study. The selection criteria stated that the families had to be able to travel to and from the university in one day. Of the 126 selected, 68 (54%) agreed to participate. Those who declined to participate had slightly higher GAs ($M_{GA} = 32.8$) than those who participated ($M_{GA} = 31.3$). 80 children of comparable age and sex were recruited from birth records at the maternity ward of the same hospital. In Table 1a-b, participant information with regard to age, sex, neonatal characteristics, demographic information, and medical information from the perinatal period for the children born preterm is presented. The children ranged from 4 to 8 years of age when they participated and all children had normal or corrected to normal vision. Three children in the prematurely born group were diagnosed with CP and in the fullterm born group one child had undergone brain surgery in infancy, one had childhood epilepsy, one had the genetic syndrome NF1, and one did not manage to complete the test battery due to excessive fussiness. These 7 children were not included in the analyses of study II and III.
**Table 1a:** Age, sex, demographic, and pre-perinatal information of the children born preterm.

<table>
<thead>
<tr>
<th>Preterm born children (N=68)</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.4</td>
<td>1.7</td>
<td>4.0-8.7</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>31.7</td>
<td>3.3</td>
<td>22.9-35.4</td>
</tr>
<tr>
<td>BW (grams)</td>
<td>1735</td>
<td>659</td>
<td>404-2962</td>
</tr>
<tr>
<td>BW standardized</td>
<td>-1</td>
<td>1.4</td>
<td>-3.9-1.9</td>
</tr>
<tr>
<td>Birth length</td>
<td>41.2</td>
<td>5.2</td>
<td>27-49</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>29.6</td>
<td>3.8</td>
<td>20.4-35.5</td>
</tr>
<tr>
<td>Apgar 10</td>
<td>8.8</td>
<td>1</td>
<td>5-10</td>
</tr>
<tr>
<td>Mother’s education (years)</td>
<td>14.3</td>
<td>2.7</td>
<td>7-21.5</td>
</tr>
<tr>
<td>Father’s education (years)</td>
<td>13.6</td>
<td>3.0</td>
<td>5-21</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>14</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

**RF pertaining to infection**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnionitis</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Infection</td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td>PPROM</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

**RF pertaining to respiration**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>RDS</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>BPD</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Respirator</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>PDA</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>NEC</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>ROP</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>GR I-II</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>GR III+</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cerebral pathology in infancy</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>IVH GR I-II</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>IVH GR III+</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>PVL</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mild abnormality non classified</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Mild</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Note:** N = number; M = mean; SD = standard deviation; GA = gestational age; BW = birth weight; SGA = small for gestational age (< 2 SD below the expected BW in relation to sex and gestational age); RF = risk factor for brain injury; PPROM = preterm premature rupture of membranes; RDS = respiratory distress syndrome; BPD = bronchopulmonary dysplasia; PDA = patent ductus arteriosus; NEC = necrotizing enterocolitis; ROP = retinopathy of prematurity; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia. Infection includes both verified and non-verified cases and examinations of ROP and cerebral pathology is only carried out in neonates born >33 gestational weeks as a standard medical procedure and the no category thus contains children who have had this examination and were healthy and those who had not received such examinations.
Table 1b: Age, sex, demographic, and neonatal information of the fullterm born participants.

<table>
<thead>
<tr>
<th>Fullterm born children (N= 80)</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>6.4</td>
<td>1.8</td>
<td>3.7</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>40.3</td>
<td>1.0</td>
<td>38-41.9</td>
</tr>
<tr>
<td>BW (grams)</td>
<td>3691</td>
<td>413</td>
<td>2910-4790</td>
</tr>
<tr>
<td>BW standardized</td>
<td>0.06</td>
<td>0.79</td>
<td>-1.68-2.12</td>
</tr>
<tr>
<td>Apgar 10</td>
<td>9.4</td>
<td>0.50</td>
<td>9-10</td>
</tr>
<tr>
<td>Mother's education (years)</td>
<td>14.7</td>
<td>2.6</td>
<td>9-25</td>
</tr>
<tr>
<td>Father's education (years)</td>
<td>14.0</td>
<td>3.1</td>
<td>9-20</td>
</tr>
<tr>
<td>n %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>36</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

Note: M = mean; SD = standard deviation; GA = gestational age; BW = birth weight.

**Study IV**

Five adolescents with varying severity of CP participated in study IV (3 male and 2 female, age range 12-17 years), two with hemiplegic CP, and three with diplegic CP. Two of the adolescents were included in the case study presented in paper IV (cases I and II). The participants were locally recruited through registration records at Kolbäcken Child Rehabilitation Centre in Umeå, Sweden. Recruitment was based on willingness to participate in the study and ability to follow instructions. Table 2 presents diagnosis, level of gross motor function, and manual ability according to the GMFCS and Manual Ability Classification System (MACS), together with additional clinical background information regarding the participating adolescents. Three participants (II, IV, and V) received upper-limb botulinum toxin treatment during the overall study period, although none of them in close conjunction with the individual training and testing period. One participant (V) received post-surgery (lower-limb) physical therapy training in parallel with participating in the present study.
Table 2: Age, diagnosis, functional severity of disability, and co-morbidities of the adolescents with CP.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>MACS</th>
<th>GMFCS</th>
<th>Affected side/ limb</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>HCP</td>
<td>II</td>
<td>II</td>
<td>Right side</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>HCP</td>
<td>II</td>
<td>I</td>
<td>Left side</td>
<td>Left sided hemianopsi</td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>DCP</td>
<td>II</td>
<td>III</td>
<td>Mainly legs</td>
<td>Autism, ID</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>DCP</td>
<td>IV</td>
<td>IV</td>
<td>Legs and arms</td>
<td>ID</td>
</tr>
<tr>
<td>V</td>
<td>13</td>
<td>DCP</td>
<td>III</td>
<td>IV</td>
<td>Legs and arms</td>
<td>ID, CVI</td>
</tr>
</tbody>
</table>

Note: HCP = hemiplegic cerebral palsy, DCP = diplegic cerebral palsy; MACS = Manual Ability Classification System; GMFCS = Gross Motor Function Classification System; ID = Intellectual disability; CVI = Cortical Visual Impairment

Methods of assessment

The included assessment methods in the empirical studies are listed in Table 3.

Table 3: Overview of the assessment methods and materials used for classification of function, handedness, cognitive function, motor control and coordination, timing training, behavior, changes in hand/arm function, medical history, and parents’ educational background used in the empirical studies.

<table>
<thead>
<tr>
<th>Materials/Methods</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth records/ journal background</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Frequency based handedness assessment</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross Motor Function Classification System</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand/arm function questionnaire</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interactive metronome</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinematic movement analysis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Manual Ability Classification System</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality assessment</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socio Economic information</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weschlers Intelligence Scale for Children- IV</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Frequency assessment of hand dominance (studies II and III)

Hand dominance was assessed by observing the children’s choice of hand when interacting with a selection of objects. The assessment tool used is based on the Edinburgh Handedness Inventory (Oldfield, 1971) and Coren and Porac’s (1980) laterality questionnaire. The children drew, cut with scissors, hammered, opened lids on a set of boxes, and threw balls. Each object was handed to the child at their midline when both their hands were free and each action was repeated 3 or 5 times. A handedness index was calculated by (R-L)/(R+L), which provides a value ranging from -1 to 1 where
negative values reflect a leftward bias and positive values a rightward bias. Values between -.3 and .3 were regarded as mixed handedness.

3-dimensional motion analyses (studies II-IV)

To assess the spatio-temporal characteristics of upper-limb movements (studies II-IV), optoelectronic recordings were made during goal-directed actions. A six-camera optoelectronic recording system (ProReflex, Qualisys Inc., Gothenburg, Sweden) was utilized. In the studies included in this thesis, only passive semi-spherical markers were used. The sampling frequency was 120Hz for all studies. Simultaneous video recordings that were time-synchronized with the optoelectronic systems were made. The information derived from these was used for clarification purposes during data processing. The 3D data was smoothed prior to the analyses with a 10 (study IV) or 12Hz (studies II-III) Butterworth filter. All 3D co-ordinates were analyzed by use of custom written software in Matlab (Mathworks Inc., Boston, MA).

Optoelectronic recording technique is one of the most precise methods available for studying movements. It is non-invasive and accessible and allows for quantification of the mechanisms of the musculo-skeletal (Capozzo, Della Croce, Leardini & Chiari, 2005) and neural systems during motion (Khutz-Buschbeck, Stolze, Jöhnk, Boczek-Funce & Illert, 1998). The system is objective and reliable if measurements are recorded in a well calibrated space and filtering and smoothing of data is applied to eliminate random errors and at least two cameras are monitoring each marker at any given time (Chiari, Della Croece, Leardini & Cappozzo, 2005). However, it is not a method without limitations. It is most precise in smaller volumes as the calibration of the space will be better: it is thus suitable for upper-limb/body movements. Soft tissue artifacts where the skin slides on top of the underlying bone are also an issue (Leardini, Chiari, Della Croce & Cappozzo, 2005). Further, marker location must be well thought through as it has been shown to affect reaching and grasping components of goal-directed movements in 3 year olds. In this study, 7mm spherical markers were attached to the distal phalanges of the index finger and thumb (Domellöf, Hopkins, Francis & Rönnqvist, 2007). Thus, optoelectronic recording methods provide a highly detailed picture of both the spatial and temporal profile of movements with a measurement error of maximum 0.5 millimeter in the studies included in this thesis.

Kinematic movement registration of this type is a method that has been applied to the study of sensorimotor development in healthy, normally developing infants and children (e.g., Rönnqvist & Domellöf, 2006; von
Hofsten, 1991) and for assessment of motor function of the upper limbs in children with CP (e.g., Chang, Wu, Wu, & Su, 2005; Domellöf, Rösblad, & Rönnqvist, 2009; Mackey et al., 2006; Rönnqvist & Rösblad, 2007). Optoelectronic methods have also been applied to the study of functional asymmetries (e.g. Hopkins & Rönnqvist, 2002). It has also been shown that movement patterns in infancy that are later associated with CP can be identified using this type of method (e.g., Nakajima, Einspieler, Marschik, Bos, & Prechtl, 2006). Hence, it is a suitable method for the objectives of this thesis.

Bead threading task (studies II and III)

The children were seated comfortably in front of a testing table. The seat was adjusted in height and distance from the table so that all children could perform the task readily. Steady support for the feet was ensured. The children were instructed to pick up small beads by use of a pincer grip and thread them onto a rod sequentially. They were further instructed to try to thread as many beads onto the rod as possible in 30 seconds picking only one bead at a time. The beads were lined up in a row 36 centimeters either to the right or the left of the rod depending on which hand was active (right side in right hand condition and vice versa for left hand condition). The distance between the beads and the rod infers midline crossings and a shift of visual focus (See figure 2a-d for experimental task and marker placement). The bead threading task was chosen for several reasons: 1) it is both challenging and engaging for children; 2) it provides an optimal experimental setup for kinematic registration of upper-body, arm and hand movements; 3) the task has been found to demonstrate both gross movement performance as well as more subtle information of spatiotemporal performance (in children with fetal alcohol syndrome, Domellöf, Fagard, Jacquet, & Rönnqvist, 2011; adolescents with Asperger’s syndrome, intellectual dysfunction, and in children with posterior fossa tumours, unpublished results). It is a unimanual task with high demands on the coordination and control of head, arm and hand/finger movements. The task involves transport (between the rod and row of beads), grip, and thread phases (fine digit control). It is also highly demanding with regards to visuomotor integration as it involves head movement control as well as gaze shifts. Accordingly, performances that are fast with high precision are assumed to reflect successful movement planning and sensorimotor integration resulting in a dynamic movement with few corrections.

The children were encouraged to perform the task 3 times with each hand, where the order was counterbalanced and randomized. All children were
allowed to practice with a few beads with each hand before the recordings commenced (the task is also described in Domellöf, Fagard, Jacquet, & Rönnqvist, 2011). A total of 9 spherical markers were affixed with skin-friendly adhesive tape to the right and left shoulders (29mm), elbows (19mm), wrists (12mm), and index fingers (7mm). A marker was also affixed to the forehead (12mm).

During the data handling process, unsuccessful trials were discarded to ensure that only trials where the task was performed without errors were subject to analysis. The onset and offset of each trial (pick-thread-to pick) were defined as the frame where the tangential velocity of the wrist marker was 60mm/s and decreasing when the active hand approached the line of beads. The video recordings were used to verify the application of these criteria. In the total prematurely born sample (study II), 2,960 (M = 46) successful pick-thread-to pick cycles were performed and 146 (4.7%) cycles were discarded due to either dropping of the bead or the child picking and threading more than one bead at a time. In the fullterm born group, a total of 4,148 (M = 55) successful cycles were performed and 203 (4.7%) cycles were discarded. When the kinematics of the preferred and non-preferred hand
were analyzed separately, the hand used for drawing was used as the preferred hand for the children qualifying, according to the frequency assessments, as mixed handed.

Extension-flexion adduction-abduction board (study IV)

To evaluate the effect of the IM intervention the participants performed a goal-directed upper-limb task before the intervention commenced (Pre-test) and at two time points after it concluded (Post-test 1 and Post-test 2). The participants were seated in front of a custom-built platform that had 10 easy to press button like light-switches (See figure 3 for task depiction and marker placement). The participants were instructed to switch on the lights in a sequential order determined by a contra-balanced block design. The goal was that all participants should perform the task with their non-affected and affected side (unimanual condition) and with both sides simultaneously (bimanual condition). The children had to begin with their hands placed at a marked starting point and press three light switches in a sequential order starting either with the light switch located closest to the body and moving forward (extension) or starting furthest away and moving back towards the body (flexion) or starting at the center and moving horizontally (adduction) or starting from the light switch furthest away in the horizontal direction and moving towards the center (abduction). The experimental design resulted in a 3 (non-affected/affected/bimanual) x 4 (extension/flexion/adduction/abduction) protocol where each direction was to be performed 3 times, resulting in a total of 36 trials for each testing occasion. The adolescents were asked to perform the task with a clenched fist as differentiated finger movements were strenuous for most of them. Two of the participants (case IV and case V) could only perform the task with their least affected side and by pushing the light switches with either the index finger (case V) or the thumb (case IV). When the trial was unsuccessful, the participant was asked to repeat the erroneous trial at the end of the related block.

For the data extraction process the velocity of the wrist marker was used. The onset of the movement was defined as the frame when the wrist marker had a velocity of 20mm/s that was increasing and the offset as the frame when the wrist marker had a velocity of 100mm/s and was increasing after the last successful light switch press. Video recordings were used as support in the application of these criteria.
Extracted kinematic parameters

Segmentation of the movement trajectory
Analysis of the segmentation of the movement trajectories was applied in studies II-V as it has been shown to be a sensitive measure of the maturity and integrity of the motor system (von Hofsten, 1991; Rönnqvist & Domellöf, 2006). Segmentations of the movement trajectory were calculated using an algorithm developed by von Hofsten (1991) where each segmentation is referred to as a movement unit (MU). An MU is defined as an acceleration phase and a deceleration phase with an accumulated increase or decrease in velocity of at least 20mm/s and an acceleration or deceleration exceeding 5mm/s² (see figure 4b-c). This algorithm (or similar ones) has been applied to several studies of development in reaching and grasping (Kuhtz-Buschbeck, Stolze, Jöhnk, Boczek-Funcke, & Illert, 1998; von Hofsten, 1991); arm movements in pre-reaching behavior (Bhat & Galloway, 2007; Bhat, Lee, & Galloway, 2007); stepping response in the newborn infant (Rönnqvist & Domellöf, 2006); arm movements in reaching and grasping in children with hemiplegic CP (Rönnqvist & Rösblad, 2007); arm movements in reaching in hemiplegic CP (Domellöf, Rösblad, & Rönnqvist, 2009; Mackey et al., 2006; Schneiberg, McKinley, Gisel, Sveistrup, & Levin, 2010); and as a stable test-retest measure of reaching in children with hemiplegic CP (Schneiberg et al., 2010).

Cumulative distance
The 3-dimensional distance of each marker was extracted to gain insight into the energy efficiency of the movement paths (see figure 4a). A shorter, more direct, movement trajectory is usually a result of maturational processes (e.g., van der Heide, Fock, Otten, Stremmelaar, & Hadders-Algra, 2005).
**Movement duration**

In studies II-IV, the actual movement time per pick-thread-to pick cycle or light switch press was extracted from the preprocessing of the kinematic data. This allowed for investigations into the movement time in relation to the measures of coordination and control. The duration of goal-directed upper limb movements has been shown to decrease as the child gets older (e.g., van der Heide, Fock, Otten, Stremmelaar, & Hadders-Algra, 2005).

As the participants varied in the number of complete movement cycles/phases they managed, all kinematic and duration data was made relative before they were subjected to statistical analysis. The mean number of MUs per complete pick-thread-to pick cycle (study II-III) and per complete light-switch press (study IV) was calculated within and across trials.

*Interactive Metronome (study IV)*

In study IV, a type of SMT method (Interactive Metronome, IM), developed to assess and train timing, was used in the intervention. This method is alleged to enhance motor functions in persons with a variety of
neurodevelopmental and neurodegenerative deviations. The method is thought to improve motor timing by integration of sensorimotor modalities through rhythmic activation (Interactive Metronome INC, Weston, Florida, USA). IM is based on synchronized rhythmic activation of upper- and lower-body extremities to a sensory signal (preset at 54 bpm but adjustable), where timing of movements can be fine-tuned via the presentation of auditory and visually presented timing error feedback. To date, few studies have scientifically evaluated the effects of IM in children. Effects on reading fluency have been found (Taub, McGrew, & Keith, 2007) and, although mainly driven by a decrease in the control group, some improvement in visual reaction time and visuo-motor control in a sample of children with attention deficit hyperactivity disorder have been shown (Cosper, Lee, Peters, & Bishop, 2009).

In study IV, the IM training regime was individually adjusted to suit the level of skill of the participant with regard to the type of action being performed, the type and amount of feedback provided, and the temporal interval of the metronome. All cases participated in 4 weeks/12 sessions of individually adjusted IM training. As the participants had different levels of ability, the IM training regime was individually adjusted to suit each participant. This resulted primarily in differences in the limbs involved and the total number of rhythmic activations (number of beats the sensor was activated on). These variations are presented in Table 4. At every training session and at the pre-test and post-test occasions, each participant performed 2 minutes (108 repetitions, 54bpm) of handclapping (bilateral for cases I-III and V; unilateral for case IV) without error feedback, and 2 minutes (108 repetitions, 54bpm) with error-feedback (all cases except case IV). This procedure allowed for assessment of rhythmic ability (without error feedback, self-phased timing) and the ability to use the error feedback provided to adjust movement timing (with error feedback).

**Table 4:** Information of the individualized IM training.

<table>
<thead>
<tr>
<th>Case</th>
<th>IM training of:</th>
<th>Total N rhythmic activations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>arms/legs</td>
<td>16,600</td>
</tr>
<tr>
<td>II</td>
<td>arms/legs</td>
<td>16,200</td>
</tr>
<tr>
<td>III</td>
<td>arms</td>
<td>13,100</td>
</tr>
<tr>
<td>IV</td>
<td>least affected arm</td>
<td>7,800</td>
</tr>
<tr>
<td>V</td>
<td>arms/ least affected arm</td>
<td>6,700</td>
</tr>
</tbody>
</table>
What is trained in the IM paradigm?

Coordination both within and between limbs are required for fast, accurate and energy-efficient movement execution. The timing of movements between different limbs (e.g. head and hand) and within limbs (e.g. shoulder, elbow, and wrist) is crucial for skilled performance in both single unit actions and in actions requiring multiple units (Schmidt & Lee, 2005).

Theoretical support for why the IM would be beneficial for movement coordination and timing stems from two sources: the pacemaker-accumulator model (PAM) and the concept of emergent timing. The PAM assumes that there is a centralized internal clock that sets a phase upon which behavior can be organized. The ticks of the internal clock are generated at a fixed frequency and they are detected by a counter. This enables precise timing of motor sequences (Koomar et al., 1998; Taub et al., 2007). Uncoordinated movements are in this theory believed to stem from a faulty pacemaker as organization and sequencing may be intact (Koomar et al., 1998). In accordance with the PAM, the timing of movements in IM is event-related and thereby a clear goal (to synchronize) exists and in the IM paradigms where no error feedback is provided one must have a temporal representation of the interval between the events (metronome beats). However, the execution of coordinated and timed movements is not just internally driven by a pacemaker but is also dependent on information from the environmental situation and the goal of the action. In IM training, most movements are supposed to be of a circular fashion with movements that are smooth and continuous (e.g., hand clapping with circular motions), which relates to emergent timing rather than event timing. In emergent timing, the ability to maintain a given interval is not dependent on or require explicit awareness of the interval duration (Schmidt & Lee, 2005). Rather, it has been hypothesized that timing under such conditions emerges from the dynamics of trajectory control (Zelaznik, Spencer, & Ivry, 2002).

Another aspect of IM is the relatively slow phase (54 bpm) at which rhythmicity and timing are usually trained. Research suggests that mental interval timing consists of two sub-systems. The automatic timing system processes discrete-event (discontinuous) timing in milliseconds and heavily involves the cerebellum. The cognitively controlled timing system deals with continuous-event timing (in seconds) that requires controlled attention and working memory and primarily involves the basal ganglia and related cortical structures (Lewis & Miall, 2006). Further, IM also entails a feedback system used as a tool to improve timing skills against the metronome. Feedback is crucial for learning a motor skill. Sources of feedback are sensory information, the result of actions, as well as augmented stemming
from other sources than the individual. Some aspects of movements are harder to evaluate using inherent (within the individual) feedback and augmented feedback in terms of how to perform the movement is necessary for improvement of skill. In IM, one can adjust the speed or trajectory of the action in accordance with the augmented feedback provided by the system to obtain a closer match to the metronome.

**Gross Motor Function Classification System (Study IV)**

The Gross Motor Function Classification System (GMFCS) (Palisano et al., 2008) was used to provide a background description of the gross motor abilities of the participants in the intervention study. In the GMFCS, ambulatory ability is in focus. For 12-18 year old children the different levels of the GMFCS refer to:

I. Walks without limitations indoor and outdoor and can climb stairs without need of support. Can run and jump but balance and coordination is impaired.

II. Can walk in most environments but usually assistance is required. For longer distances a wheelchair may be needed. Can climb stairs with assistance.

III. Can walk with hand-held mobility assistance and needs assistance when moving from sitting to standing. Can use an electronic wheelchair and climb stairs with assistance.

IV. Uses a wheelchair in most environments but can walk shorter distances indoors with support. Can provide support with the legs when being moved in standing position. Need of a wheelchair that provides pelvic and upper body support. Uses an electrical wheelchair but can sit in a manual for assisted transportation.

V. Is transported in all environments by use of a wheelchair. May possibly be able to use an electronic wheelchair if it is well adjusted. Has limited control of the head, upper body, legs and arms. Cannot provide support with the legs when being moved.

**Manual Ability Classification System (Study IV)**

As with the GMFCS, the Manual Ability Classification System (MACS) (Eliasson et al., 2006) was used as a background description of the children’s functional ability of the hands. The GMFCS is a tool for judging how well the child with hemiplegic CP can use their hands when handling objects important in daily activities. It should be used to reflect self-initiated ability and should measure normal functional level, not maximum performance. As it has been developed for use with children with hemiplegic CP, bi-manual
ability is measured. In the present study, however, it was also applied to children with diplegic CP.

The MACS classifies manual ability into the following 5 levels:

I. Handles objects with ease and with good results. Can have some limitations in tasks that require speed and precision. Such limitations does not limit the child’s independence in performing daily activities and are limited to finger dexterity/ hand coordination and control in the handling of heavy, fragile, new, or fine objects.

II. Handles most objects but with some limitation with regard to quality and/or speed. Some activities may be avoided or may be performed but with limitations. The limitations do usually not limit the child’s ability to perform daily activities although some tasks may be adjusted to ease performance. Can perform the same activities as in level I but slower and with poorer quality. Usually uses environmental support to ease performance (may for example use surfaces as support) and differences between the hands in functional level may limit the effectiveness in performance.

III. Has impairments in the handling of objects and require assistance in preparation and/or adjustment of activities. The performance is slow with limited success with regard to quality and quantity. Can perform adjusted tasks independently.

IV. Can handle a limited number of objects in adjusted situations. Can perform parts of activities with effort and limited success. Require continuous support and help and/or adjusted equipment in order to perform parts of activities.

V. Cannot handle objects and have severely limited ability to perform simple actions. Is totally dependent on assistance. May be able to participate in activities by means of for example, pushing buttons.

Arm/hand function questionnaire (study IV)

To acquire information about the subjective experience of change in tonus and function of the affected (in cases I-III) and least affected (in cases IV-V), arm/hand a questionnaire was devised. Questions probed experiences of changes in muscle tone, ability to get dressed, ability to feed, and the ability to use the arm/hand in daily activities and recreation. Questions about changes in finger dexterity and in the functional level of the least affected/affected arm/hand were also asked. The children and their parents graded the changes as; (5) substantially positive change, (4) somewhat positive change, (3) unchanged, (2) somewhat negative change, (1) substantially negative change. Open questions were asked to gain
information about experiences of improved or worsened function, improved or worsened function in the legs, and what effect (if any) was of most importance. Finally, a question if the child had been involved in any other type of training was asked, either during or after the IM training had finished. The questionnaire was for the parents and the child to fill out together and it was administered immediately after the IM training was completed and 3 and 6 months after completion of training.

Socioeconomic information (studies II-III)

The parents of the children were asked a number of questions pertaining to the socioeconomic status of the family. Questions about family structure (if the parents were married, cohabitants or separated; mother as only caregiver; father as only caregiver; other primary caregiver; other family constellation; number of siblings), mother’s profession, father’s profession, years of education of the mother and the father (starting from first grade).

Wechsler’s Intelligence Scale for Children (study III)

To assess the cognitive function of the fullterm and prematurely born children in study III the Wechsler’s Intelligence Scale for Children, 4th edition (WISC-IV) was administered. The tests included in the WISC-IV are grouped into four cognitive domains: verbal comprehension (verbal intelligence quotient, VIQ), perceptual reasoning (performance IQ), working memory, and processing speed. These four domains together constitute the full scale IQ which is an expression of general intelligence. The WISC-IV assessment was made by professionals with previous experience of administration of the test and other types of neuropsychological assessments of children. The testing was carried out in a quiet room, free from possible distracting materials. A shorter break was taken halfway through the testing session to ensure the children’s sustained attention throughout all included tests. The WISC-IV is a test that is extensively used for children between 6-16 years-of-age in clinical practice and for research purposes.

Journal background/ medical birth history (studies II-IV)

In studies II-III, information from the children’s medical birth records was extracted. This information was used both as background factors to describe the children included in the studies and as factors included in the analyses of the outcome data (see Tables 1a-b and 2 for background information). In study IV, the journals from the associated rehabilitation center were used to gain insight into the presence of any co-morbidities and results from the
children’s MRI scans, if they had received such. This information was solely used to provide a more robust case description.

**Statistical methods**

All statistical analyses in studies II-IV were carried out using Statistica 9. Table 5 is a summary of the statistical methods used in the empirical studies.

**Table 5:** Summary of the statistical methods applied in the empirical studies.

<table>
<thead>
<tr>
<th>Statistical methods</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilcoxon matched pairs test</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>T-test</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson’s $\chi^2$</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Pearson’s correlations</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Analysis of covariance</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple hierarchial linear regression</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Multivariate analysis of covariance</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effect sizes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohens $d$</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Pearson’s correlations</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Partial Eta square, $\eta_p^2$</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study II**

In study II, the children born preterm were divided into three sub-groups based on their GAs (moderately preterm; M-PT = 33-35, $n = 35$; very preterm; V-PT = GW 29-32+6, $n = 17$; extremely preterm; E-PT = < 28 GWs, $n = 12$). The outcomes were analyzed by means of analysis of covariance (ANCOVAs), multivariate analysis of covariance (MANCOVAs), Pearson’s $\chi^2$, and Pearson’s correlations. The kinematic outcomes were analyzed primarily by MANCOVAs where side (preferred/non-preferred) and group (E-PT, V-PT, M-PT, and fullterm; FT) were used as categorical predictors. Separate ANCOVAs were performed on the kinematic outcomes to investigate side effects within GA groupings. Age was used as a continuous covariate in these analyses. Person’s correlations were used to further analyze the effect of age within the sub-groupings. Significant effects were followed up by means of ‘unequal numbers honestly significant difference’ post-hoc analysis and partial eta square ($\eta_p^2$) was used as effect size estimate. Pearson’s $\chi^2$ was used to test the difference in the frequency of non-right handedness between the group of children born preterm and the FT born children. Significant results are reported on the level of < .05, < .01 and, < .001.
Study III

Between group (prematurely vs. fullterm born) analyses of IQ were carried out on the index values derived from the WISC-IV (verbal index, performance index, working memory index, perceptual speed index, and full scale IQ) by means of t-tests (two-tailed). The kinematic outcomes of interest were also subjected to t-tests to establish presence of any group differences. Cohen's d was used as a measure of effect size on the outcomes from the t-tests. Hierarchical multiple linear regressions within the prematurely and fullterm born groups were conducted to explore the relationship between movement kinematics and full scale IQ. GA (within the prematurely born group only), sex and full scale IQ were used as predictors in the analyses. In the prematurely born group GA was imputed in the first step, sex in the second step, and IQ in the third. In the fullterm born group, sex was imputed in the first step, followed by full scale IQ. The alpha level was set at $p < .05$ in all analyses. Standardized Beta ($\beta$), R Square change ($\Delta R^2$), F change, and p values are reported.

Study IV

In study IV, the kinematic outcome was analyzed on trial level where each trial was paired with the corresponding trial at all three testing occasions. Wilcoxon matched pairs tests were used as data was not normally distributed. The alpha value was set at 0.025 (0.05/2) to correct for the increased risk of type I errors as there were repeated analyses. Where outcomes were statistically significant, Pearson’s correlation coefficient was used to calculate an effect size. The uni- and bimanual conditions were analyzed separately by side (affected/non-affected). Due to measurement errors and premature onset of movement, 17 trials were discarded. A total of 105 trials for case I and a total of 104 for case II were subjected to statistical analysis.

Ethical considerations

The children, adolescents and their parents were informed verbally and in writing about the purposes and the contents of the studies. The parents of the participating children gave informed consent in writing regarding study participation and access to medical journals. All empirical studies were approved by the Umeå Regional Ethical Board and were carried out in accordance with the Declaration of Helsinki.
SUMMARY OF RESULTS AND BRIEF DISCUSSION OF FINDINGS

Study I

The existence of increased rates of non-right handedness in children born preterm is unclear as several studies, assessing handedness both directly or indirectly as a background variable, have shown inconsistency in their findings.

The research questions posed in study I were therefore:

i. Do children born preterm have higher occurrence of non-right handedness than children born fullterm?

ii. Is non-right handedness associated with neurological deviations and/or neuropsychological findings in children born preterm?

These questions were investigated through a systematic literature review and a meta-analysis including 18 studies (1,947 cases, 8,170 controls). Odds ratio (OR) calculations for dichotomous data revealed an OR of 2.12 ($p < .0001$; significant heterogeneity at 51%) in favor of non-right handedness in the prematurely born populations included in the meta-analysis (see figure 3). This corresponded to a percentage of non-right handedness of 22% in the children born preterm and 12% in the control groups. Studies with higher quality scores of how handedness was assessed and in the description of their samples had higher cumulative ORs (2.45 and 2.55, respectively with 0% heterogeneity in both) than did those with low quality scores (1.70 and 1.52, respectively with significant heterogeneity at 74% for handedness assessment alone). The lack of significant heterogeneity between the high quality studies suggests that studies having less refined measures of hand preference, less well defined study samples, and less well-matched control groups, less information about participant background, demographics and parental background, less rigorous study design, and less refined recruitment processes had larger variations in study outcome than those studies that had high levels of control and more refined assessment methods.
Figure 5: Random-effects odds ratio (OR) meta-analysis for non-right handedness in cases and controls. The size of the study marker corresponds to study weight. 95% confidence interval (CI) is represented by error bars. The weighted cumulative OR (open diamond) of non-right handedness significantly favors cases. * = unpublished data.

When assessing the occurrence of publication bias using Duval and Tweedie’s trim-and-fill method (Duval & Tweedie, 2000). Seven studies were imputed to the left (in favor of controls) of the cumulative point estimate which was adjusted to 1.66. However, visual inspection of the funnel plot indicates that no “small study” effect was apparent as the imputed studies did not cluster at the bottom of the plot. As only six out of 18 of the included studies had a focus on studying handedness in children born preterm and no apparent small study effect is present, the finding of an OR of 2.12 in favor of cases may be regarded as a secure result.

In the literature review, it was revealed that 12 (Allin et al., 2006; Caldú et al., 2006; Kesler et al., 2006; Lancefield et al., 2006; Marlow et al., 1989; Nosarti et al., 2004; O’Callaghan et al., 1993; Powls et al., 1996; Ross et al., 1987, 1992; Saigal et al., 1992; Zuazo, Garaizar, & Prats, 1999) of the included studies attempted, either as a primary research question or as a control measure, to relate handedness to neurological outcomes. This was done with the rationale that non-right handedness may be related to early occurring brain injury in the children born preterm. Of these, only two of the studies were able to show such a connection (O’Callaghan et al., 1993; Saigal et al., 1992). O’Callaghan and colleagues (1993) showed an association between left handedness and the number of risk factors for brain injury and
in the study by Saigal and colleagues (1992) an association between non-right handedness and neurological impairments was shown.

Based on the findings that preterm birth is associated with increased risk of brain injury (Volpe, 2009) and the hypothesis that non-right handedness may be caused by such insults (Bakan, 1971, 1977), the occurrence of non-right handedness may also be related to neuropsychological functioning. Increased rates of left hand preference has been shown to be related to lower IQ scores, impaired motor abilities, and difficult temperament in 4 year old children (O’Callaghan et al., 1993). Ross and colleagues similarly found lower IQ scores and delayed language development in 4 year old prematurely born non-right handed children (1987). The connection between lower IQ scores and non-right handedness persisted at 7-8 years of age, where an association between attention deficit hyperactivity disorder and non-right handedness was shown (Ross et al., 1992). A linear relationship between cognitive level and hand preference score, where increased level of non-right handedness was related to lower cognitive scores, was found by Marlow and colleagues (2007). However, several studies have not been able to show a connection between non-right handedness and neuropsychological outcomes (Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Powls et al., 1996; Saigal et al., 1992; Zuazo et al., 1999).

The findings from the meta-analysis suggest that preterm birth, at least in some instances, is associated with disturbance of the typical development of cerebral asymmetry related to hand preference. However, for most children born preterm (78%) in this meta-analysis, a typical right handed preference is established. It is possible that the differences in hand preference reported in studies are related to sample heterogeneity as suggested by Bishop (1990). It is, for example, possible that the expression of non-right handedness is more prominent in children born most immaturely. Some of the studies included in the meta-analysis that focused on children with an extremely preterm birth or with an extremely low BW (< 27 GWs, < 1,000 grams) were also able to show the highest incidences of non-right handedness (e.g., Marlow, Hennessy, Bracewell, & Wolke, 2007; Marlow et al., 1989). Less skillful motor performance was shown by a few studies (O’Callaghan et al., 1993; Ross et al., 1992). Children born with a BW of less than 1,500 gram with a non-right hand preference have also been shown to have poorer manual skills than right handed children born with a comparable BW (Powls et al., 1996). Similarly, poorer writing skills were shown in children with low gestational age (32-34 GA) and extremely low GA (< 27 GWs) even though most of the children were right handed. Sagnol et al., (2007) showed a lack of side differences in terms of movement time in 5 year old children born preterm compared to controls. It is possible that the diminished frequency of
right handedness in children born preterm does not directly reflect a reverse handedness pattern (i.e. left handedness) but rather a lack of specialization. This could be due to the occurrence of brain injury and/or developmental delay. At present, it appears that non-right handedness is more prevalent in children born preterm but the underlying causes and mechanisms for this phenomenon remain unclear.

**Study II**

The aim of study II was to investigate hand preference and side specific specialization in terms of spatio-temporal organization of upper-body movements in a group of children born preterm (≤35 GWs) at 4-8 years of age. Four specific hypotheses and one exploratory research question were posed. These were as follows:

The children born preterm compared to their fullterm born peers were hypothesized to:

i. show less evident hand preference in terms of the frequency of hand use when manipulating objects.

ii. have movement trajectories that are more segmented, longer in 3D distance, and have longer durations.

iii. have less evident side specialization as expressed by less smooth and coordinated hand/arm trajectories.

iv. have increased segmentation and movements of the head.

Of further interest was to explore if the results from the above stated hypotheses were influenced by GA.

As a measure of control, the effect of sex on all kinematic outcomes were analyzed by means of MANCOVAs where age at testing was used as a continuous covariate and side (preferred/non-preferred) x sex (boy/girl) x group (prematurely born/fullterm born). Sex was only significant as a main effect on the number of MUs of the head \( F(1, 265) = 20.59, p < .001, \eta^2_p = 0.03; \) girls, \( M = 256, SD = 108; \) boys, \( M = 313, SD = 120. \) Thus, due to the general lack of overall effects of sex on the outcome variables and the limited sample size as well as the unequal number of girls and boys in the groups with the lowest GAs, sex was not included as a categorical predictor in the analyses in study II.
Analyses of the frequency-based assessment of handedness showed that 85% of the children born preterm and 93% of the fullterm born children were right-handed. When the index values derived from the frequency-based assessment were statistically tested, no significant results were noted (see Table 6 for mean values, standard deviations, and p values) for any of the groups or ages.

**Table 6.** Mean values and standard deviations of the laterality index and category of hand preference presented by group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lat index- hand</th>
<th>RH</th>
<th>MH</th>
<th>LH</th>
<th>NRH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
</tr>
<tr>
<td>FT (n = 76)</td>
<td>0.76</td>
<td>0.35</td>
<td>71 (93)</td>
<td>3 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>M-PT (n = 35)</td>
<td>0.73</td>
<td>0.42</td>
<td>32 (91)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>V-PT (n = 17)</td>
<td>0.50</td>
<td>0.60</td>
<td>12 (71)</td>
<td>2 (12)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>E-PT (n = 13)</td>
<td>0.55</td>
<td>0.48</td>
<td>11 (85)</td>
<td>1 (8)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Overall PT (n =65)</td>
<td>0.63</td>
<td>0.49</td>
<td>55 (85)</td>
<td>4 (6)</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>

*Note:* Lat. = laterality; M = Mean; SD = standard deviation; M-PT = moderately prematurely (PT) born; V-PT = very PT born; E-PT = extremely PT born; FT- fullterm born.

It has been suggested that increased rates of non-right handedness, in terms of the hand chosen when performing manual skillful tasks, may reflect early occurring disruption of brain development (Bakan, 1971; Bishop, 1990; Satz, 1972; Soper & Satz, 1984), possibly caused by birth complications (Coren, 1995). Others have stressed that preterm birth itself is associated with increased rates of non-right handedness (e.g., Marlow et al., 2007; Ross et al., 1987). It is possible that events associated with preterm birth are related to changes in atypical hemispheric organization. However, no significant difference in hand preference was apparent in this study although the children born < 33 GWs did have a lower mean value on the laterality index of the hand. The frequency-based assessment of handedness showed that 85% of the children born preterm and 93% of the children born fullterm were right-handed.

Regarding movement performance and side specificity, only the fullterm born children expressed such a difference in movement duration and movement segmentation of the head and wrist where the preferred side was faster and smoother than the non-preferred side (see Table 7 for mean values and standard deviations on the kinematic outcome parameters presented by group. Outcomes are further presented by side and overall).
Table 7: Mean values and standard deviations of the kinematic outcomes by group, overall and side.

<table>
<thead>
<tr>
<th>Group</th>
<th>Side</th>
<th>3D distance (mm)</th>
<th>Movement Units (n)</th>
<th>Duration (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wrist M SD</td>
<td>Head M SD</td>
<td>Wrist M SD</td>
</tr>
<tr>
<td>FT (n = 76)</td>
<td>Pref</td>
<td>862 252</td>
<td>272 96</td>
<td>10.9 4.6</td>
</tr>
<tr>
<td></td>
<td>N-pref</td>
<td>855 159</td>
<td>274 94</td>
<td>11.8 4.7</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>858 210</td>
<td>273 95</td>
<td>11.4 4.7</td>
</tr>
<tr>
<td>M-PT (n = 35)</td>
<td>Pref</td>
<td>826 89</td>
<td>252 80</td>
<td>11.0 4.7</td>
</tr>
<tr>
<td></td>
<td>N-pref</td>
<td>819 89</td>
<td>266 86</td>
<td>11.1 3.4</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>822 88</td>
<td>259 83</td>
<td>11.0 4.1</td>
</tr>
<tr>
<td>V-PT (n = 17)</td>
<td>Pref</td>
<td>945 185</td>
<td>337 143</td>
<td>15.7 9.0</td>
</tr>
<tr>
<td></td>
<td>N-pref</td>
<td>931 175</td>
<td>323 144</td>
<td>15.8 8.8</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>938 177</td>
<td>330 142</td>
<td>15.8 8.8</td>
</tr>
<tr>
<td>E-PT (n = 12)</td>
<td>Pref</td>
<td>882 106</td>
<td>310 115</td>
<td>14.9 6.0</td>
</tr>
<tr>
<td></td>
<td>N-pref</td>
<td>880 114</td>
<td>320 117</td>
<td>13.7 4.6</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>881 108</td>
<td>315 114</td>
<td>14.3 5.3</td>
</tr>
</tbody>
</table>

Note: FT = fullterm born; PT = prematurely born; M-PT = moderately PT; V-PT = very PT; E-PT = extremely PT; mm = millimeter; s = seconds; Pref = preferred; N-pref = non-preferred

In terms of movement kinematics, as expected, the children born preterm took longer time to complete a pick-thread-to pick cycle and had increased segmentation of the movement trajectories of the wrists compared to their fullterm born peers. The post-hoc analyses of these parameters showed that the effect was located between the children born fullterm and moderately prematurely and the children born very and extremely prematurely. The latter two groups had more segmentations and longer durations than did the groups with children born fullterm and moderately preterm. Similarly, the children born preterm had more segmentations of the head and longer 3D distances with the effect being located to the very prematurely born children, possibly indicating increased looking and/or postural instability. Thus, the increased segmentations and longer movement durations in the children with lower GAs (< 33 GWs) possibly reflect developmental delay or deviation in motor control. Similar associations between GA and motor skill have been reported (O’Callaghan et al., 1993).

There were large age effects within all groups of children on all kinematic outcome parameters, where the older children expressed faster, smoother, and shorter movement paths (see figure 6a-d for examples of the association between age and some kinematic outcomes). Such changes in movement control with age are consistent with previous findings in 4 to 12 year old children (Kuhtz-Buschbeck et al., 1998) and probably reflect improved
motor planning and increased maturation of the brain systems supporting such actions.

Figure 6a-d: Correlations, regression line shown, between age at testing and mean number of movement units and 3D distance of the wrist during performance with the preferred (a and c respectively) and non-preferred (b and d respectively) side for the fullterm (FT), moderately preterm (M-PT), very preterm (V-PT), and extremely preterm (E-PT) born children. The r value (Pearson’s correlation coefficient) and its significance level are shown by group within each graph. The x axis denotes age at testing in both graphs.

To summarize, the group differences observed between the children born preterm and fullterm were located to the children born before GW 33. This group of children had less well organized and controlled movements and had lower laterality indexes as well as no clear side specificity in terms of movement performance. The children born moderately preterm performed equally well as the fullterm born children and had a pattern of side-specific movement organization that was similar to that of the fullterm born children. The observed findings may indicate that the children born very preterm (< 33 GWs) who are more immature at birth have a higher risk of adverse brain development resulting in more disorganized movements. Further, it is possible that a developmental delay is more prominent in this group of children.
Study III

The aim of study III was to investigate differences in intellectual function and movement performance between children born preterm and children born fullterm at 6-8 years of age. Further, the associations between general intellectual function (full scale IQ) and kinematic outcomes when controlling for GA and sex were of interest. The hypotheses were as follows:

i. There are significant differences in IQ scores and upper-body goal-directed movement kinematics between the prematurely and fullterm born children, where the children born preterm have lower IQ scores and more disorganized movement trajectories.

ii. There is a relation between measures of general intellectual function (full scale IQ) and the efficiency of upper-body movement kinematics in the children born preterm after controlling for GA and sex.

As hypothesized, the children born preterm had significantly lower IQ scores than their fullterm peers. The children born preterm in this study had scores that were in the normal range ($M = 94.5$), confirming previous findings (e.g., Bhutta, 2002). No significant differences were found between the children born preterm and the children born fullterm in any of the kinematic outcome variables. Thus, the first hypothesis could only in part be supported.

In the hierarchal regression analyses of the children born preterm GA was entered in the first step, sex in the second step and full scale IQ in the third step. This allowed control for the effects of GA and sex in the examination of the predictive capacity of IQ on the kinematic parameters. GA (entered in the first step) was shown to be a significant predictor for the duration of the preferred wrist ($\Delta R^2 = 12.9\%$), 3D distance of the non-preferred wrist ($\Delta R^2 = 16.6\%$), and MUs of the preferred wrist ($\Delta R^2 = 15.8\%$). Full scale IQ (after controlling for GA and sex) contributed a significant proportion of unique variance to the prediction of the duration of the preferred wrist ($\Delta R^2 = 11.8\%$) and MUs of the preferred wrist ($\Delta R^2 = 17.7\%$). Note that the $\Delta R^2$ was reduced from the first step to the third for duration on the preferred wrist suggesting that GA alone was a better predictor for this kinematic outcome. Within the group of children born preterm, sex did not contribute any unique variance to any of the kinematic outcome parameters. Full scale IQ only added unique variance to the predictions of the duration and segmentation (MUs) of the movement trajectories on the preferred side (see...
Table 8). Within the fullterm born group, a significant effect for sex was revealed on the 3D distance of the head when the non-preferred side was active.

**Table 8:** Multiple hierarchical linear regression analyses predicting movement kinematics from IQ in the children born preterm.

<table>
<thead>
<tr>
<th>Kinematic parameter</th>
<th>Predictor</th>
<th>β</th>
<th>ΔR²</th>
<th>F change</th>
<th>p value</th>
<th>p value whole model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (pref wrist)</td>
<td>GA</td>
<td>-0.238</td>
<td>0.129</td>
<td>4.442</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-0.037</td>
<td>0.000</td>
<td>0.006</td>
<td>0.939</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.365</td>
<td>0.118</td>
<td>4.390</td>
<td>0.045</td>
<td>0.044</td>
</tr>
<tr>
<td>Duration (non-pref wrist)</td>
<td>GA</td>
<td>-0.216</td>
<td>0.074</td>
<td>2.410</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-0.097</td>
<td>0.007</td>
<td>0.229</td>
<td>0.636</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.180</td>
<td>0.029</td>
<td>0.897</td>
<td>0.352</td>
<td>0.344</td>
</tr>
<tr>
<td>3D distance (pref wrist)</td>
<td>GA</td>
<td>-0.221</td>
<td>0.106</td>
<td>3.566</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.087</td>
<td>0.011</td>
<td>0.371</td>
<td>0.547</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.304</td>
<td>0.082</td>
<td>2.857</td>
<td>0.102</td>
<td>0.097</td>
</tr>
<tr>
<td>3D distance (non-pref wrist)</td>
<td>GA</td>
<td>-0.287</td>
<td>0.166</td>
<td>5.963</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.141</td>
<td>0.027</td>
<td>0.956</td>
<td>0.336</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.343</td>
<td>0.104</td>
<td>4.151</td>
<td>0.051</td>
<td>0.018</td>
</tr>
<tr>
<td>MUs (pref wrist)</td>
<td>GA</td>
<td>-0.250</td>
<td>0.158</td>
<td>5.640</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-0.041</td>
<td>0.000</td>
<td>0.005</td>
<td>0.943</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.447</td>
<td>0.177</td>
<td>7.435</td>
<td>0.011</td>
<td>0.009</td>
</tr>
<tr>
<td>MUs (non-pref wrist)</td>
<td>GA</td>
<td>-0.086</td>
<td>0.044</td>
<td>1.387</td>
<td>0.248</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-0.025</td>
<td>0.000</td>
<td>0.000</td>
<td>0.997</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.374</td>
<td>0.124</td>
<td>4.172</td>
<td>0.051</td>
<td>0.155</td>
</tr>
<tr>
<td>3D distance (head pref side)</td>
<td>GA</td>
<td>-0.232</td>
<td>0.105</td>
<td>3.504</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.277</td>
<td>0.086</td>
<td>3.066</td>
<td>0.091</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.245</td>
<td>0.053</td>
<td>1.962</td>
<td>0.172</td>
<td>0.047</td>
</tr>
<tr>
<td>3D distance (head non-pref side)</td>
<td>GA</td>
<td>-0.212</td>
<td>0.063</td>
<td>2.005</td>
<td>0.167</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.167</td>
<td>0.030</td>
<td>0.953</td>
<td>0.337</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.096</td>
<td>0.008</td>
<td>0.253</td>
<td>0.619</td>
<td>0.388</td>
</tr>
<tr>
<td>MUs (head pref side)</td>
<td>GA</td>
<td>-0.091</td>
<td>0.026</td>
<td>0.814</td>
<td>0.374</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.032</td>
<td>0.002</td>
<td>0.062</td>
<td>0.805</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.209</td>
<td>0.039</td>
<td>1.164</td>
<td>0.290</td>
<td>0.576</td>
</tr>
<tr>
<td>MUs (head non-pref side)</td>
<td>GA</td>
<td>-0.123</td>
<td>0.045</td>
<td>1.402</td>
<td>0.246</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>0.004</td>
<td>0.000</td>
<td>0.014</td>
<td>0.908</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FSIQ</td>
<td>-0.264</td>
<td>0.062</td>
<td>1.933</td>
<td>0.175</td>
<td>0.360</td>
</tr>
</tbody>
</table>

*Note:* FSIQ, full scale intelligence quotient from the Wechsler Intelligence Scale for Children 4th edition (WISC-IV); GA, gestational age; MU, movement unit; pref = preferred. Duration is in seconds.

Hence, full scale IQ adds unique variance to the prediction of movement kinematics within the group of children born preterm alone that is over and above the variance explained by GA and sex. However, the amount of variance explained is limited for both GA and full scale IQ (maximum 17.7%). In combination (the models with significant outcomes considered), however, the variance explained from these three variables ranged from 13.9 to 33.5%. This suggests that there are several other sources where variance in outcome may stem from, including natural differences in maturation.
In summary, the children born preterm show lower full scale IQ scores than their fullterm born peers. The full scale IQ scores are associated with aspects of movement performance even when the important influence of GA is controlled for. No relations between IQ and movement organization were evident in the fullterm born group. The associations between movement kinematics and cognitive functions within the group of children born preterm suggest shared neural underpinnings and interrelated development of these functions.

**Study IV**

In study IV the aim was to explore possible short- and long-term effects of the Interactive Metronome (IM) on aspects of spatio-temporal organization of upper-body movements in CP.

We asked whether timing and rhythmicity training with the IM of adolescents with hemiplegic CP would:

i. result in improved timing and rhythmic ability both with and without error feedback.

ii. have effect on the spatio-temporal properties of goal-directed upper-body movements.

iii. continue to have effects on timing/rhythmicity and/or spatio-temporal properties of goal-directed upper-body movements at 6 months after completed training.

The focus in this section will be on the results from the outcomes of the adolescents presented in paper IV (cases I and II) but data from the other three participants will also be presented for comparative purposes.

Results of timing and rhythmic ability from the IM instrument showed that cases I and II were both able to learn to adjust and synchronize their movements to better match the metronome beat. Case I had improved timing/rhythmic ability both when error feedback was given and when it was not (see figure 7a). Case II showed a higher degree of reliance on error feedback for closer synchronization and a lower degree of learning when no error feedback was given (see figure 7b). The effects were maintained at the
Post-test 2 testing occasion for both cases. Learning was not shown by cases III-V (see figure 7c-e).

Figure 7a-e: Outcomes from the IM training instrument at pre-test, post-test 1, and post-test 2 occasions.

Similar changes in timing and rhythmic ability as expressed by cases I and II has also been shown in other studies (Shaffer et al., 2001; Sommer & Rönnqvist, 2009; Taub et al., 2007). It is possible that the changes in timing and rhythmic ability detected by the IM instrument relate to neuronal plasticity mechanisms of the sensorimotor system (Nudo, 2006). Another possibility is that such changes are related to improvements in the ability to
sustain attention as the IM training system incorporates such elements for success.

Kinematic changes of the wrist were found on both the affected and the non-affected side for case I and primarily on the non-affected side for case II. In general, the effects were located on the non-affected side in the unimanual condition and the affected side in the bimanual condition and were largely maintained at Post-test 2 (see graphical representation of outcomes in figure 8 and 9 for MUS and duration respectively). Such changes lead to a more energy-efficient movement trajectory. The changes in duration and segmentation remained (or emerged) at post-test 2 for both participants. For cases I, II, IV and V, movement segmentation and movement duration decreased which can be interpreted as an indication of increased movement control and/or reduced biomechanical constraint. Mean number of MUs and mean duration by side and test occasion for each case is presented in figure 8 and 9 respectively. Case II had fewer noticeable changes in the kinematic parameters included than did case I, which could possibly be explained by the lower level of learning of timing/rhythmicity when no error signals were provided. Case III showed no changes in terms of MUs or duration, possibly related to a failure to learn the task and/or the co morbidity of autism and intellectual dysfunction. In terms of 3D distance, some significant changes were noted, where movement trajectories became longer (case V) and shorter (cases II and III on the non-preferred/non-affected side).

Figure 8: Mean number of MUs presented by side for the Pre-test, Post-test 1, and Post-test 2 occasion for the cases in study IV. Note: * = p < .05; ** = p < .05; *** = p < .05
In terms of the subjective experience of changes in arm and hand function, cases IV and V reported substantial and somewhat substantial changes in muscle tone, movement speed, and increased range of movements. With regard to the open questions, both cases reported positive changes in abilities associated with daily living (getting dressed, controlling the electronic wheelchair, controlling the computer, etc.). These changes remained, albeit somewhat reduced, at post-test 2. As cases IV and V only had some control over the movements of one arm, it is a possibility that they experienced these changes as the trained arm was the arm used in activities. In hemiplegic CP, the affected arm is usually not engaged in activities and is usually the targeted arm/hand in constraint-induced movement therapies (e.g., Craje et al., 2010).
GENERAL DISCUSSION, FUTURE PROSPECTS AND CONCLUSIONS

The main objectives of this thesis were to investigate hand preference, general and side specific goal-directed upper-body movement performance in terms of movement organization in children born prematurely compared to children born fullterm. Further, the association between upper-body movement performance and cognitive function, gestational age, and sex in these groups of children were of interest. Another objective was to explore if and how sensorimotor training affects the organization of upper-body kinematics in adolescents with CP (study IV). The occurrence of non-right handedness in children born preterm was investigated by means of an odds ratio meta-analysis (study I), where case-control studies reporting the frequency of handedness in their samples were included. Handedness, by means of frequency observations of the hand selected in unimanual tasks, and side specificity, in terms of movement kinematics during goal-directed upper-body movements, was investigated (study II) in 4-8 year old children born preterm and in an age-matched fullterm born comparison group. The association between the kinematics of upper-body goal-directed movements and intellectual function was explored in 6-8 year old prematurely and fullterm born children (study III).

Differences between the groups of children born preterm and fullterm

Hand preference

The findings presented in study I in this thesis show that the occurrence of non-right handedness is doubled in populations of children born preterm. This doubling corresponded to 22% occurrence of non-right handedness in the prematurely born populations. Although the prevalence of a non-right hand preference was shown to be heightened in children born preterm the findings also implies that the majority of these children establish a right hand preference. Results in line with this finding were shown in study II, where the majority (85%) of the children born preterm expressed a right hand preference. However, it appears that the groups with the lowest GAs (< 33 GWs) have higher rates of non-right handedness and the lowest handedness index values. When statistically testing the frequency of handedness category within the groups and when testing the index values, only trends towards significance were shown \( (p = .08 \text{ and } .09) \). It is possible
that we could not show a significant difference in hand preference as we had a relatively small study sample, specifically in the lower GAs. The finding of higher frequencies of non-right handedness in the lower GAs may be related to the higher occurrence of risk factors associated with brain lesions in these groups and/or maturational aspects of brain development (Volpe, 2008, 2009). This suggestion is in line with the theory proposed by Bakan (1971) which suggests that early disruptions in brain development cause non-right handedness. However, a recent study using a large sample (10,000 children at the age of 10) could not establish a link between strength or direction of hand preference (i.e., degree of right or left handedness) and the occurrence of birth stressors including measures pertaining to respiration, circulation, and signs of cerebral injury. What this study did show was that birth stressors were associated with cognitive and behavioral problems (Nicholls et al., 2012). These findings suggest that the theory proposed by Bakan (1971) may be incorrect.

Others have proposed that genetic factors and early disruptions in brain development may be underlying increased rates of non-right handedness in prematurely born children (Annett, 1985; Bishop, 1990). In relation to the findings of increased rates of non-right handedness and decreased strength of hand preference reported in the thesis, a plausible explanation is, at least in part, to be found in epigenetics. Both preterm birth and handedness have been shown to be heritable to some degree (Annett, 1985; Clausson, Lichtenstein, & Cnattingius, 2000) suggesting involvement of genetic mechanisms. Another possible explanation, although speculative, is that preterm birth affects the function of the neurons so that the brain becomes less plastic, which has been shown by Pitcher and colleagues (2011), and a result of this may be that a dominant and more specialized hand is harder to establish. Such a mechanism could of course also be of genetic origin. It would be interesting, in line with Bakan, Dibbs, and Reed (1973), to investigate the possibility that families with an aggregated rate of non-right handedness also have an aggregated rate of preterm births. Such an endeavor requires a population based approach where a large number of people with a non-right hand preference could be recruited.

**Movement organization**

Group differences between the children born < 33 GWs and the age-matched fullterm born comparison groups at 4-8 years of age were found in movement organization in terms of movement duration, 3D-distance, and the number of segmentations of the movement trajectories (study II). The children born moderately preterm performed as well as their fullterm born
peers. These findings suggest that the greater vulnerability of more immature children in terms of the often increased occurrence of detrimental medical complications and the less mature central nervous system, have long-term consequences for sensorimotor development. The differences in movement kinematics were found for both the wrist and head. Possible explanations for these findings are: 1) a general developmental delay in sensorimotor functions, 2) persistent sensorimotor control deficits, 3) visuo-perceptual deviances related to the functions of specifically the dorsal visual stream (Atkinson & Braddick, 2007; Dutton, 2003). Of course, only developmental studies employing a longitudinal approach can uncover whether the findings reflect a developmental delay or persistent deficit. It would be interesting to include tests tapping into dorsal stream functions in future studies of prematurely born children as this would further the understanding of how sensorimotor control is affected by visuo-spatial and motion perception. Of interest would also be to further study the kinematic data used in studies II and III from a movement dynamics perspective where head (eye) and hand coordination is explored. Such an approach would allow disentangling the degree of visual guidance of the hand that is needed.

**Intellectual function**

In study III, children of 6-8 years of age from study II who had participated in WISC-IV testing were included. It was shown that the groups differed on the full scale IQ, verbal and, perceptual indices. The children born preterm, as a group, had lower test scores in general compared to their fullterm peers. The mean differences between the groups ranged from 5 to 7 points, which can be regarded as functionally quite a small difference; however, the effect sizes were moderate to large suggesting consistency within the groups. These findings are in accordance with previously reported lower scores on IQ tests (e.g., Allin et al., 2001, 2011; Bhutta, 2002; Hoff Esbjerg, Hansen, Greisen, & Mortensen, 2006; Kontis et al., 2009; Peterson et al., 2003; Soria-Pastor et al., 2009). Possible deviations underlying lowered IQ scores in children born preterm have been suggested to be lesions of the type found in the diffuse form of PVL, where myelination of the cerebral WM is affected (Volpe, 2009). Studies investigating the relationship between results from high resolution magnetic resonance imaging and IQ measures are needed to further the understanding of this relationship.

The largest difference between the children born preterm and the children born fullterm was found on a test of auditory working memory (letter-number sequencing). This test places high demands on attention, processing speed, sequencing, and auditory short-term memory. Although the
prematurely and fullterm born groups did not differ on the working memory index. The finding from the letter-number sequencing test warrant further investigation of executive functions and processes and their relation to aspects of sensorimotor performance, including action planning and motor learning. Intellectual function (full scale IQ) was associated, when controlling for the effect of GA and sex, with duration and segmentation of the movement trajectories of the preferred wrist in the preterm born children. No such relation was shown for the children born fullterm. This suggests that approaches where cognitive aspects of movement coordination and control are included may be shown to be an important line of enquiry when studying sensorimotor function and its deviations in children born preterm. Further, as IQ was shown to be a unique predictor of many of the kinematic outcomes when controlling for GA and sex, further variance may be explained if future research involves other measures known to have effect on IQ, such as maternal education and other socio-economic variables.

The influence of age, GA, and sex

Age substantially influenced the kinematic outcomes in study II, where movements became faster, smoother, and shorter with increasing age. This effect was shown in all groups of children but the children born very and extremely preterm had the steepest regression lines. Thus, in this data, group differences in movement performance appear to be largest for the youngest children, and gradually decreases with age to be non-significant at the age of 7-8. Indeed, in study III, where an older (6-8) subsample of the children in study II was included, no group differences were shown for any of the kinematic outcomes. Possible explanations for this effect could be a developmental delay that is most prominent in the youngest (4 years of age) and most prematurely born children. True developmental studies (i.e., longitudinal approaches) are needed to verify whether there is a differential developmental effect within the groups. In terms of hand preference, age did not influence the strength of the handedness index, indicating that the children in general had an established side preference by the age of 4. This finding is in accordance with results reported by Rönnqvist and Domellöf (2006), where children of 3 years of age were shown to express a hand preference in terms of the hand chosen when reaching and grasping.

Effects of GA were shown in both studies II and III. In study II, the children born < 33 GWs exclusively explained group differences between the children born preterm and fullterm. Thus, children born after 33 GWs performed equally well, on a group level, as the fullterm born comparison children. GA also influenced the movement kinematics in study III, where effects were
shown on the segmentation and duration of the movements, specifically on the preferred wrist in the group of children born preterm. Thus, even though no difference between the children born preterm and fullterm were shown in movement kinematics in study III, the outcome in the prematurely born group was clearly influenced by GA.

The influence of sex on kinematic outcomes was limited in study II and controlled for in study III. In study III, it was shown that sex explained no unique variance in movement performance within the group of prematurely born children. However, this does not mean that sex may not influence the kinematic outcome. Sex was imputed after GA in the models which implicates that any shared variance of sex and GA may be “eaten up” by the first imputed variable, thus allowing the first step to account for most variance. Male sex has been shown to be a risk factor for CP (Beaino et al., 2011), preterm birth (Di Renzo, Rosati, Sarti, Cruciani, & Cutuli, 2007), and also for sensorimotor deviances in preterm born children (e.g., Whitaker et al., 2006). Hence, investigations of the effect of sex or accounting for its variance may prove important in future studies.

Handedness: a dichotomy between preference and performance?

In study II, the only difference between the preferred and non-preferred side in terms of movement performance was found in the fullterm born group on measures of duration and segmentation of the movement trajectories. This result is in line with findings reported by Triggs and colleagues (1997; 2000). We found that when the preferred hand was performing the task, the movements were faster, the wrist and head had less segmentation than when the non-preferred hand carried out the task. Thus, kinematic information related to the organization and proficiency of movements derived from optoelectronic recordings is sensitive enough to detect subtle side differences. Implicated in this finding is that handedness (preferred/non-preferred) in terms of the frequency of hand use may not be a good indicator of movement performance per se as most children in the prematurely born group had an established right hand preference. As with the strength of the indices derived from the handedness inventory and the increased rates of non-right handedness in the groups with the lowest GAs (< 33 GWs), interestingly, the differences found between the groups in movement kinematics were located to these groups too. As previously discussed, it is possible that larger sample sizes, specifically in the low GAs, would have yielded a significant difference in the laterality index as well. The children
born < 28 GWs showed signs of reversed asymmetry in terms of movement performance, where the preferred hand appeared to be more disorganized than the non-preferred hand. There is a need for detailed studies aimed at investigating the relation between side specificity and movement performance from a developmental perspective. This would increase the understanding of what role an established hand preference plays in fine and skillful movement specialization. As the knowledge about the neural mechanisms underlying the establishment of handedness is limited, such studies would also benefit this research area.

Training of sensorimotor functions

Timing training and constraints

In study IV, the two participants with hemiplegic CP showed relatively good initial timing ability as assessed by the IM instrument. They also showed stable and evident improvement in timing and rhythmic ability over the training period and their improved timing remained six months after completed training. The adolescents with more severe diplegic CP (not presented in the paper) showed no such improvements. A possible explanation for this discrepancy is that 1) the efficiency and/or accessibility of IM training may depend on the severity of a person's condition and associated individual constraints, or that 2) the IM instrument is not suited to detect such changes in persons with severe forms of movement impairments. Reduced accessibility to the IM in persons with CP may derive from deficits in the interpretation and amount of information available from sensory systems as well as in proprioception and the control over muscle groups needed for successful performance (e.g., Ricken et al., 2006). The deviations in motor control may pose a specific problem with accessibility to the IM as timing has been shown to emerge as a by-product of the dynamics of trajectory control (Zelaznik, Spencer, & Ivry, 2002). As most movements in the IM training method applied in the present study should be smooth, continuous, and circular in fashion (e.g. hand clapping with circular motions), the emergent timing properties deriving from the trajectory control require the ability to perform such movements correctly. As such, an inability to produce movements with emergent timing elements, due to the internal and/or external constraints of the individual, may be a specific limitation. Regarding the second point, the adolescents with hemiplegic CP did show some short- and long-term improvements in movement kinematics as did two of the adolescents with more severe forms of CP. This indicates that there might be possible training effects of the IM that are not detected
by the instrument itself. However, it remains unclear if it is the timing training properties or the repeated activation embedded in the IM training or a combination of the two that have effects on movement activation and control.

Feedback in sensorimotor learning

An element embedded in the IM training program that is important in motor learning is feedback. In IM, feedback of movement performance is provided visually and through audition where the magnitude and temporal direction (early or late) of the error form the basis for movement correction. Hence, the feedback system in IM provides the information required for error and reinforcement motor learning (Wolpert, Diedrichsen, & Flanagan, 2011). Effective and accurate sensory input and the processing of such are required for skilled actions (Wolpert et al., 2011). Thus, the explicit form of presentation of errors in IM may be particularly beneficial for persons with CP as sensory information may, and/or the interpretation of such is often impaired. The ability to learn motor skills through feedback in children with hemiplegic CP has been shown to be governed by the same principles as in the population without such impairments (Hemayattalab & Rostami, 2010). How motor learning is modulated by feedback in more severe forms of CP and the effect of co-morbidities is an understudied area of research.

Motor planning or biomechanical constraints?

Impairments in motor planning have been implicated in children with CP, where kinematic analyses have shown deficits in end-state control (Crajé, Aarts, Nijhuis-van der Sanden, & Steenbergen, 2010; Steenbergen & Gordon, 2006; Steenbergen, Verrel, & Gordon, 2007) and compensatory motor actions (postural involvement, longer movement durations etc.) to increase end-state control (Butler, Ladd, Louie, et al., 2010; Butler, Ladd, Lamont, & Rose, 2010; Domellöf, Rösblad, & Rönnqvist, 2009; Mackey, Walt, & Stott, 2006; Rönnqvist & Rösblad, 2007). The kinematic data (movement duration, MUs, and 3D distance) extracted from the 3D motion analyses in study IV can collectively be used to analyze aspects of motor planning. The reduction in segmentation, and in some instances 3D distance and movement duration could be interpreted as improvements in planning ability. However, other reasonable explanations are improved motor control and release of biomechanical constraint. However, despite the origin of the kinematic changes, more energy-efficient movements were observed.
Methodological considerations

Children born preterm have frequently been shown to have increased rates of movement deviances as detected by standardized motor function test batteries (e.g., Edwards et al., 2011; Williams et al., 2010; de Kieviet et al., 2009). Optoelectronic recordings are reliable and sensitive to detect small changes in motor control (as discussed in the methods section). The application of this observational technique to the study of movements allows for the extraction of detailed information pertaining to coordination and control of movements. As the system is reliable under the correct conditions and simply monitoring and recording marker placement over time, the validity and reliability of studies utilizing it relate to the task that is used and the information extracted. In the studies included in this thesis, care was taken to have relatively constrained tasks in terms of how they were performed to reduce within- and between-subject variability. In terms of movement kinematics, group differences were detected in study II although none of the children had diagnosed motor problems and in study IV, kinematic changes after SMT training was detected. A step that is necessary to take to further the understanding of the added value of kinematic movement registrations is to include standardized motor function test batteries to enable comparisons between the methods.

In terms of the kinematic information extracted, movement duration and movement segmentation were measures where most group differences were noted. It is possible that the 3D distance is more sensitive to choice of strategy where movements with longer distances do not necessarily imply that they are less well controlled and organized as has been suggested (Rönnqvist & Domellöf, 2006; Schmidt & Lee, 2005). It is possible, although speculative, that 3D distance becomes decoupled from other aspects of movement control (MUs) with development, as the correlation between age and 3D distance is lower than between age and MUs, specifically for the wrist in the fullterm group in study II (see figure 6c-d). MUs are very sensitive to on-line corrections (von Hofsten, 1991) and future research involving children with CP should also include the relative size of the MUs as the movement profile most likely involves several small corrections but also larger jerk-type movements. Information about the size of the movement may aid in the prospect of teasing apart biomechanical constraints from aspects related to movement planning in children with CP, where larger corrections possibly reflect the former and smaller corrections the latter.

A unifying issue embedded in all the kinematic studies included in this thesis is the test-retest reliability of the tasks. This is specifically an issue within the intervention study (study IV), where the evaluation of the SMT method
applied (IM) was primarily focused on changes of goal-directed upper-body movement kinematics. Future studies must include a control group or multiple pretests to ensure baseline stability. Despite the limitations with kinematic movement registrations, the application of this method allows for the extraction of more information than can be seen with the naked eye. It is sensitive and reliable and has, as applied in this thesis, been shown to be able to detect group and side differences as well as age effects.

**Future prospects and conclusions**

The findings presented in this thesis implicate long term effects of preterm birth on movement organization and control, and intellectual function. In general, the children born most prematurely were shown to have both lower IQ and more disorganized movements compared to the prematurely born children with higher GAs and the children born fullterm. Additionally the children born at very low GAs also showed less side specific movement performance and had higher rates of non-right handedness implicating effects of preterm birth on cortical organization and/or sensorimotor learning mechanisms. Several studies have shown that children born prematurely, without major disability, have persistent and substantial sensorimotor deviances (e.g., Edwards et al., 2011, de Kieviet et al., 2009) and lower scores on cognitive tests (e.g., Bhutta, 2002). Of course, a lower functional sensorimotor and cognitive level, even when only mild, can be a barrier to both scholastic and personal achievements. Thus investigations into the etiology and interrelatedness of these functions are an important area of research. Further, applied research into the effects of sensorimotor training on movement performance, executive function and aspects of cognition in groups of children and adolescents where seemingly small changes can be of relevance for individual autonomy is of importance. As was shown in study IV, SMT resulted in improvements in movement organization and, importantly, the subjective experience of change and improvement was substantial for a number of the participants.

The findings presented in the thesis raise several important questions that have implications for future research. These questions are primarily related to study sample characteristics, study design, and the associations between outcome measures. In the following sections, what I believe to be some of the most central issues and the prospects that I would like to investigate in the future are summarized.
The role of intellectual function in movement organization

As intellectual function (full scale IQ) was shown to be associated with movement performance in the prematurely born population alone, it important to further the study of this relationship within this group of children. Of interest would be to investigate executive aspects of movement performance i.e., movement planning, inhibition of a prepotent response, motor learning, and on-line corrections in response to perturbations. Further, investigations into how performances on tasks like these relate to outcomes on standardized executive function tests would be of interest as it would enable disentanglement of cognitive aspects from movement performance. Cognition in action. Such an endeavor would benefit from including the visuo-perceptual approach. Specifically dorsal stream functions as it is highly involved in reach and grasp behaviors and has been shown to be dysfunctional in children born very preterm (e.g., Atkinson & Braddick, 2007). Further, the development of a side or hand preference and how it is related to sensorimotor learning, and other types of learning, is of interest. It is a possibility that deviances in neural plasticity mechanisms, as shown by Pitcher and colleagues (2011), could at least in part offer an explanation for the lack or reduction of side specificity in terms of hand preference and movement organization as observed in studies I and II. Of course, it would be specifically valuable if future studies were carried out longitudinally. It is further of importance that future studies also aim at improving control over possible confounding factors, specifically those related to socio-economic variables and pre-perinatal risk factors. To enable this level of control, larger study samples are needed or control can be improved by using stratified samples that are comparable on possible confounding factors.

The role of sensory and proprioceptive information in movement organization

Movement performance relies not only on motor output but is tightly coordinated and interrelated with vision, tactile input, and proprioception. It is further influenced by the goal of the movement, task constraints, the environment it occurs in and, as shown in study III, by intellectual function. What happens if we occlude visual information? What is the effect if proprioceptive information is altered? How important is the sensory information for movement performance? What will the effect on movement kinematics be if the cognitive, attentive, or inhibitory demand is higher? What will the effect be if the task has high demands on sensorimotor learning? It would be of interest to further develop the kinematic tasks used,
and to develop new sensitive out-of-the-laboratory sensorimotor tasks, to try to tease these aspects apart.

**The role of larger study populations**

As evident from studies II and III, GA influences motor outcome significantly, where the children born most prematurely (< 33 GWs) have the poorest motor outcomes. To elucidate why this group appears to be most negatively affected in terms of movement performance, attempts at identifying specific factors associated with this group of children is of importance. A promising place to start is to investigate the role of risk factors that may be more prominent in this group of children. Larger samples than those included here are needed for this endeavor. Further, a longitudinal approach would be preferable as it would be possible to distinguish between developmental delay and more permanent sensorimotor deviation. Further, a population based study of non-right handed mothers would be relevant to further the understanding of the underlying factors associated with the apparent increased rate of non-right hand preference in the prematurely born populations shown. This approach would allow for investigations of whether this group of women has an increased risk of preterm labor and also familial aspects of hand preference.

**The advancement of synchronized metronome training studies**

By including multiple pretests or a control group, the results from SMT studies in children and adolescents with CP would be strengthened. Further, the cognitive aspects of movement control should be distinguished from biomechanical aspects within this group to increase understanding of the effects of SMT. Functional magnetic resonance imaging could be applied in the attempt to answer this question. As the IM training method places high demands on attention and sensorimotor learning, tests related to these functions should also be included. If, for example attention, is trained in SMT it is important to find out whether training of this function is driving the observed changes in motor performance. Further, it would be of interest to apply the IM method on preterm born children with developmental coordination disorder, and other groups that may benefit, as the task constraints of IM (motions related to emergent timing) would be reduced for this group compared to children and adolescents with CP.
REFERENCES


infancy: From sensation to cognition. (pp. 191–236). East Sussex: Psychology Press.


