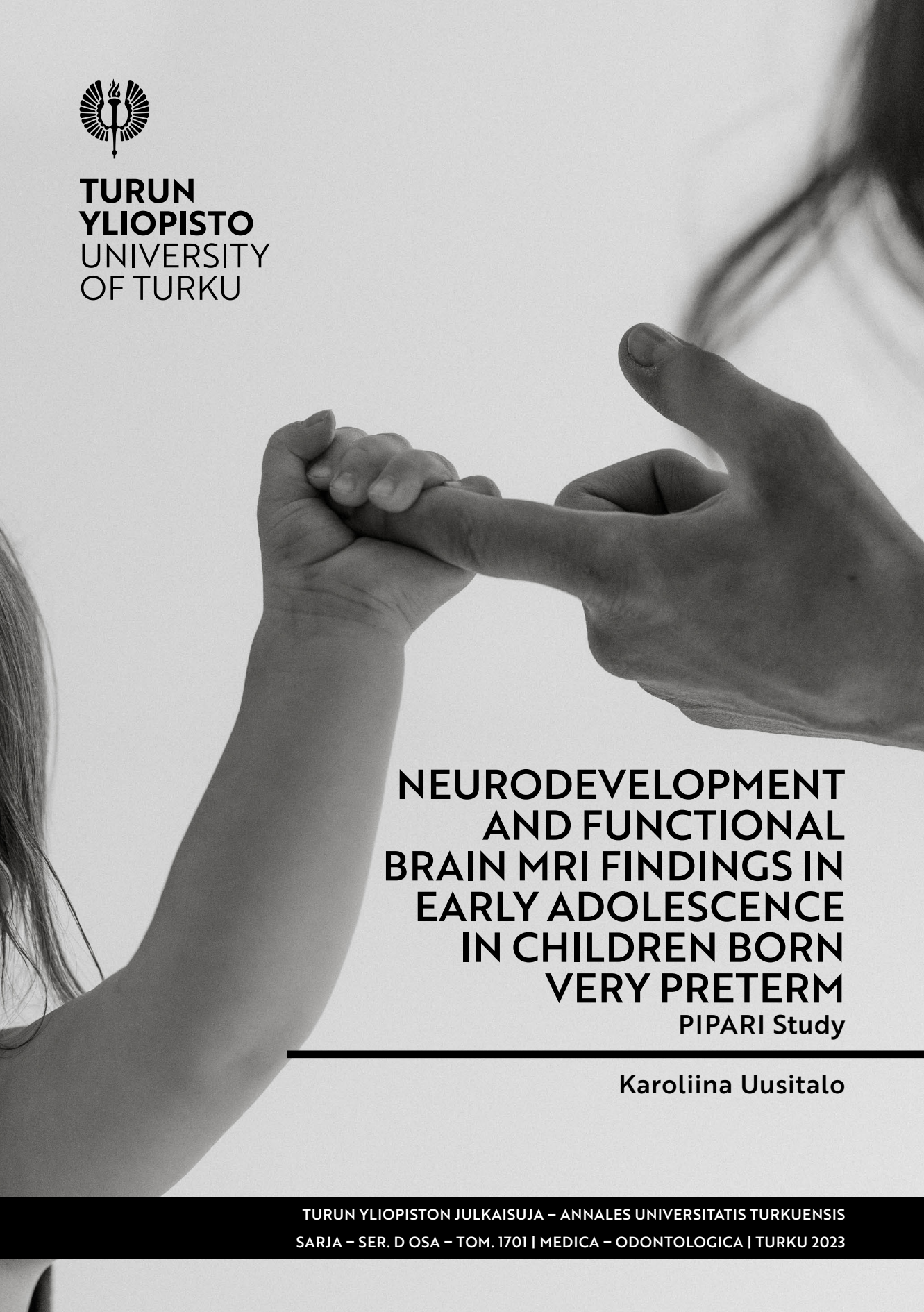

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# NEURODEVELOPMENT AND FUNCTIONAL BRAIN MRI FINDINGS IN EARLY ADOLESCENCE IN CHILDREN BORN VERY PRETERM

## PIPARI Study

Karoliina Uusitalo

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1701 | MEDICA – ODONTOLOGICA | TURKU 2023

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*To my family*

UNIVERSITY OF TURKU
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KAROLIINA UUSITALO: Neurodevelopment and functional brain MRI findings in early adolescence in children born very preterm – PIPARI Study
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## ABSTRACT

Very preterm birth has shown to increase risk for adverse neurodevelopment. Despite the decreased rate of cerebral palsy (CP), neurodevelopmental impairments other than CP are still common in children born preterm. This thesis is part of the multidisciplinary PIPARI follow-up study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) of infants born very preterm. It includes three original studies that present data regarding long-term neurodevelopmental outcomes and functional brain magnetic resonance imaging (fMRI) findings of the children born very preterm (birth weight ≤1500 grams and/or gestational age <32 weeks) born in 2001–2006.

The first aim of this thesis was to study the motor outcome at 11 years and its association with concurrent cognitive outcome and health-related quality of life. The second aim was to study the association between neurological examination at 2 years of corrected age and neurodevelopment at 11 years. The third aim was to study the hand coordination skills of 13-year-old adolescents born very preterm and full-term controls, and to assess brain activation in fMRI during these hand coordination tasks.

This thesis showed that motor impairment other than CP was still common in children born very preterm and that motor impairment was associated with adverse cognitive outcome and lower self-experienced health-related quality of life at 11 years of age. The neurological examination at 2 years was associated with cognitive outcome at 11 years of age. The fMRI findings at 13 years showed that, although the clinical performance of hand coordination tasks was similar in adolescents born very preterm and controls, the task-related brain activation was stronger in adolescents born very preterm compared to the controls born full-term.

KEYWORDS: cerebral palsy, developmental coordination disorder, minor neurological dysfunction, cognitive development, motor development, neurological development, quality of life, brain magnetic resonance imaging, preterm children

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Lääketieteellinen tiedekunta
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## TIIVISTELMÄ

Pikkukeskosuus lisää poikkeavan pitkäaikaiskehityksen riskiä. CP-vamman esiintyvyys pikkukeskosilla on vähentynyt, mutta CP-vammaa lievemmät neurologisen kehityksen häiriöt ovat edelleen yleisiä. Tämä väitöskirja on osa moniammatillista PIPARI-seurantatutkimusta (PIeniPAinoisten RIskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään). Väitöskirja sisältää kolme alkuperäistutkimusta, jotka kuvaavat vuosina 2001–2006 pikkukeskosena syntyneiden pikkukeskosten (syntymäpaino ≤1500 grammaa ja/tai gestaatioikä <32 viikkoa) pitkäaikaista kokonaiskehitystä ja toiminnallisia aivokuvantamislöydöksiä.

Väitöskirjan tavoitteena oli tutkia motorista kehitystä ja sen yhteyttä kognitiiviseen kehitykseen ja itse koettuun terveyteen liittyvään elämänlaatuun 11 vuoden iässä. Toisena tavoitteena oli tutkia kahden vuoden korjatussa iässä tehdyn neurologisen tutkimuksen yhteyttää neurologiseen, motoriseen ja kognitiiviseen kehitykseen 11 vuoden iässä. Kolmantena tavoitteena oli tutkia hienomotorisia taitoja ja hienomotoristen tehtävien aikaisia toiminnallisia aivokuvantamislöydöksiä pikkukeskosena syntyneillä ja täysaikaisena syntyneillä nuorilla 13 vuoden iässä.

Väitöskirjatyö osoitti CP-vammaa lievemmän motoriikan häiriön olevan edelleen yleinen ja yhteydessä heikompaan kognitiiviseen kehitykseen ja koettuun terveyteen liittyvään elämänlaatuun 11-vuotiailla pikkukeskosilla. 2-vuotiaana tehty neurologinen tutkimus oli yhteydessä kognitiiviseen kehitykseen vielä 11 vuoden iässä. Kliinisesti arvioituna 13-vuotiaat pikkukeskosena syntyneet nuoret suoriutuivat hienomotorisissa tehtävissä verrokkien tavoin, mutta hienomotoristen tehtävien aikainen aivoaktivaatio oli voimakkaampaa pikkukeskosena syntyneillä.

AVAINSANAT: CP-vamma, kehityksellinen koordinaatiohäiriö, lievä neurologinen toimintahäiriö, kognitiivinen kehitys, motorinen kehitys, neurologinen kehitys, elämänlaatu, aivojen magneettikuvantaminen, keskosuus

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# Abbreviations

| | |
|---|---|
| ADHD | attention-deficit/hyperactivity disorder |
| AUC | area under the curve |
| BOLD | blood oxygenation level dependent |
| CP | cerebral palsy |
| DCD | developmental coordination disorder |
| DCDQ'07 | Developmental Coordination Disorder Questionnaire 2007 |
| EACD | European Academy of Childhood Disability |
| fMRI | functional magnetic resonance imaging |
| GMA | Prechtl's Assessment of General Movements |
| GMFCS | Gross Motor Function Classification System |
| HINE | Hammersmith Infant Neurological Examination |
| HRQoL | health-related quality of life |
| IQ | intelligence quotient |
| MND | minor neurological dysfunction |
| Movement-ABC 2 | Movement Assessment Battery for Children – Second Edition |
| MRI | magnetic resonance imaging |
| ROC | receiver operating characteristic |
| ROI | region of interest |
| SD | standard deviation |
| SINDA | Standardized Infant NeuroDevelopmental Assessment |
| WISC-IV | Wechsler Intelligence Scale for Children – Fourth Edition |
| 17D | 17-dimensional illustrated questionnaire |

# List of Original Publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Uusitalo K, Haataja L, Nyman A, Ripatti L, Huhtala M, Rautava P, Lehtonen L, Parkkola R, Lahti K, Koivisto M, Setänen S, on behalf of PIPARI Study Group. Preterm children's developmental coordination disorder, cognition and quality of life: a prospective cohort study. *BMJ Paediatr Open*. 2020 Apr 6;4(1):e000633. doi: 10.1136/bmjpo-2019-000633. PMID: 32518843; PMCID: PMC7254160.

II Uusitalo K, Haataja L, Nyman A, Lehtonen T, Setänen S, on behalf of PIPARI Study Group. Hammersmith Infant Neurological Examination and long-term cognitive outcome in children born very preterm. *Dev Med Child Neurol*. 2021 Aug;63(8):947–953. doi: 10.1111/dmcn.14873. Epub 2021 Apr 8. PMID: 33834473.

III Uusitalo K, Haataja L, Saunavaara V, Lind A, Vorobyev V, Tilli J, Parkkola R, Setänen S; on behalf of PIPARI Study Group. Performance in Hand Coordination Tasks and Concurrent Functional MRI Findings in 13-Year-Olds Born Very Preterm. *Pediatr Neurol.* 2021 Oct;123:21–29. doi: 10.1016/j.pediatrneurol.2021.07.001. Epub 2021 Jul 10. PMID: 34339952.

# 1 Introduction

The survival rate of infants born preterm has increased due to advanced perinatal care during the past decades (Groenendaal et al., 2010). Children born very preterm have an increased risk for neurodevelopmental impairments (Brydges et al., 2018; Pascal et al., 2018). Although the prevalence of cerebral palsy (CP) has decreased in high-income countries regardless of gestational age (McIntyre et al., 2022), it has been reported that the rate of motor impairments other than CP has increased in children born extremely preterm (Spittle et al., 2018).

Neurological examination of the infant, from term age to 12 months of age, has shown to predict neurodevelopmental outcome at 2 years of corrected age in children born preterm (Hadders-Algra et al., 2019; Setänen et al., 2014). Further, it has been shown that CP can be diagnosed even before 5 months of age by combining the data from neurological examination and brain magnetic resonance imaging (MRI) (Novak et al., 2017). However, early developmental scales might underestimate the rate of subsequent neurodevelopmental impairments other than CP (Pascal et al., 2018). Thus, early identification of children at risk for these impairments has remained a challenge. Children born very or extremely preterm have an increased risk for poorer academic achievement as well as social and emotional problems compared to peers born at term (Alterman et al., 2022; Linsell et al., 2019; van Beek et al., 2022). This underlines the importance of long-term follow-up in children born very preterm, even in the absence of CP.

This thesis focused on assessing the long-term neurodevelopment i.e. neurological, motor, and cognitive outcomes in children born very preterm and studying the association between the early neurological examination and the neurodevelopment at 11 years of age. In addition, this thesis evaluated the hand coordination skills and concurrent functional brain MRI findings in adolescents born very preterm and controls born full-term.

# 2 Review of the Literature

## 2.1 Preterm birth

According to World Health Organization, preterm birth is defined as being born before 37 weeks of pregnancy. In 2014, the estimated worldwide preterm birth rate was 10.6%, equating to 14.8 million liveborn preterm infants (Chawanpaiboon et al., 2019). In the USA, the preterm birth rate is 12–13%, and in Europe and other developed countries preterm birth rates from 5% to 9% are reported (Goldenberg et al., 2008). In Finland, the rate of preterm birth in 2021 was 5.9% equating to 2912 children and the rate of very preterm children (<32 weeks of gestation or birth weight <1501g) was 0.8% equating to 382 children (THL, 2021).

Preterm birth can be categorized as spontaneous i.e. due to spontaneous preterm labour or premature rupture of membranes, or initiated i.e. by labour induction or caesarean delivery for maternal or fetal indications. Even though many factors increase the risk for preterm birth, the causal pathways are not fully understood. (Goldenberg et al., 2008.) Preterm birth can also be classified based on gestational age: extremely preterm birth (<28 weeks of gestation), very preterm birth (<32 weeks of gestation) and moderate to late preterm birth (32 to 37 weeks of gestation); and according to the infants' birth weight: extremely low birth weight (<1000g), very low birth weight (<1500g), and low birth weight (<2500g). The term small for gestational age can be used if the infants birth weight is <-2 standard deviations (SD) or <10th percentile of the mean birth weight.

Preterm birth rates have been shown to have increased in some high-income countries (Chawanpaiboon et al., 2019). A report from 11 high-income countries, including Finland, showed that the mortality and major morbidities in children born vey preterm decreased between 2007 and 2015 (Lui et al., 2019). When interpreting preterm birth rates and their consequenses, it is important to keep in mind that the majority of the studies are based on preterm populations in these high-income countries, even though 80% of the preterm births occur in low-income and middle-income countries in Asia and sub-Saharan Africa (Chawanpaiboon et al., 2019).

## 2.2 Neurodevelopmental outcome

Children born very preterm have an increased risk for an adverse neurodevelopmental outcome including neurological, motor and cognitive impairments (Hirvonen et al., 2017; Nyman et al., 2017; Pascal et al., 2018; Setänen et al., 2016; Spittle et al., 2018, 2017). A decline in the prevalence of CP has been reported, irrespective of the gestational age (Smithers-Sheedy et al., 2022). Nevertheless, it is important to recognize neurodevelopmental impairments other than CP as well, as these impairments commonly co-occur and have negative effects on academic achievement and behavioral and social functioning (Blank et al., 2019; Broström et al., 2018; Latal, 2009).

### 2.2.1 Neonatal factors affecting neurodevelopment

Lower gestational age and birth weight are related to an increased rate of CP and severe cognitive impairment during the first years of life (Brydges et al., 2018; Pascal et al., 2018; Smithers-Sheedy et al., 2022). The influence of a decreasing gestational age and birth weight on subsequent neurodevelopmental outcome seem to become less robust during childhood and adolescence (Brydges et al., 2018; De Kieviet et al., 2009). Within the children born very preterm, those born small for gestational age have higher risk for mortality and cognitive impairment than very preterm peers born appropriate for gestational age (Guellec et al., 2011). Male sex has also shown to be a prognostic factor for poorer cognitive development and motor impairments other than CP (Linsell et al., 2015, 2016).

The effect of neonatal morbidities for neurodevelopmental outcome is widely studied. Bronchopulmonary dysplasia has shown to associate with motor impairments and cognitive deficits in children born preterm (Cheong & Doyle, 2018). Neonatal sepsis has been associated with an increased risk for neurodevelopmental impairments in toddlers born very preterm, but the data on long-term neurodevelopmental effects of neonatal sepsis is limited (Cai et al., 2019). Surgically managed necrotizing enterocolitis is reported to associate with adverse neurodevelopmental outcome (Hintz et al., 2005). The mere presence of patent ductus arteriosus has shown not have an impact on the long-term neurodevelopmental outcome, including cognitive development, academic achievement, and behavior, in children born ≤37 weeks of gestation (Collins et al., 2018). However, infants born extremely preterm with primary patent ductus arteriosus surgery have been shown to have an increased risk for neurodevelopmental impairment at 6 years of age compared to their extremely preterm peers who received drug treatment for patent ductus arteriosus, including those who had patent ductus arteriosus surgery after the prior drug treatment (Gudmundsdottir et al., 2020).

### 2.2.2 Neuromotor outcome

Motor impairments are among the most frequently reported adverse long-term outcomes in children born very preterm (De Kieviet et al., 2009). The level of motor impairment can range from mild to severe, CP being the most severe motor disability. In children born very preterm, the estimated rate of motor delay was 21% at approximately 2 years of corrected age (evaluated with developmental scales) and 36% at preschool age (evaluated with the Movement Assessment Battery for Children) (Pascal et al., 2018). One proposed explanation for this age-dependent change may be that the early developmental assessments (for instance Bayley Scales of Infant and Toddler Development, Third Edition), commonly used to evaluate the motor outcome at 2 years of age, seem to underestimate the rate of subsequent motor impairments since they assess current levels of motor development whereas later assessments evaluate more specific tasks of motor functioning (Pascal et al., 2018). Another explanation might be that motor development of children born very preterm appears to have a tendency to catch up spontaneously during the first years of life, and it has been suggested that the attainment of early motor milestones is easier compared to more advanced motor skills (De Kieviet et al., 2009).

#### 2.2.2.1 Cerebral palsy

CP is a term used to describe a group of permanent motor disorders that affect movements and posture and cause activity limitation. The causes behind these disorders are nonprogressive injuries occurring in the brain during the perinatal period. The motor disorder of CP is often accompanied with disturbances to sensation, perception, cognition and behavior. In addition, epilepsy and secondary musculoskeletal problems are associated with CP. (Rosenbaum et al., 2007.)

The reported overall prevalence rate of CP is 0.2–0.4% (Colver et al., 2014). Preterm birth is a well-known risk factor for CP and the rate of CP is reversely associated with gestational age and birth weight (Pascal et al., 2018; Smithers-Sheedy et al., 2022). A recent Australian study including children born in 2013–2014 reported that the rate of CP was 3.4% in children born <28 weeks of gestation, 2.6% in children born 28–31 weeks of gestation, 0.4% in children born 32–36 weeks of gestation, and 0.08% in children born ≥37 weeks of gestation (Smithers-Sheedy et al., 2022). A Finnish national register study of children born between 2001–2008 showed that by 7 years of age the rate of CP was 3.7% in children born at <32 weeks of gestation, 1.4% in children born at 32–33 weeks of gestation, 0.3% in children born at 34–36 weeks of gestation and 0.1% in children born ≥37 weeks of gestation (Hirvonen et al., 2014).

Early detection of CP is essential to ensure appropriate intervention that aims to optimize the motor and cognitive outcome, prevent and minimize secondary

impairments, and to support the carers' well-being and mental health (Novak et al., 2017). Brain pathologies in neonatal brain imaging, including intraventricular hemorrhage and periventricular leukomalacia, are strongly predictive for CP in children born very preterm (Linsell et al., 2016). Cranial ultrasound is widely used assessment in neonatal intensive care setting for scanning infants born preterm or at term, however, it is not suitable to determine the exact location or extent of all lesions (Bosanquet et al., 2013; Wezel-Meijler & de Vries, 2014).

Abnormal MRI findings have been reported in 86% of the children with spastic or dyskinetic CP (Krägeloh-Mann & Horber, 2007). In high-income countries where the neonatal MRI is available, CP can be reliably diagnosed before 5 months of corrected age by utilizing the medical history, standardized neurological and motor assessments, and neuroimaging (Novak et al., 2017). The tools with highest predictive validity for CP are the Prechtl Qualitative Assessment of General Movements (GMA) (sensitivity 98%, specificity 91%), the Hammersmith Infant Neurological Examination (HINE) (sensitivity and specificity 90%) and MRI at term (sensitivity 86% to 100%, specificity 89% to 97%) (Bosanquet et al., 2013; Novak et al., 2017; Romeo et al., 2016). The combination of abnormal GMAs or HINE scores with abnormal MRI has been reported to be more accurate in predicting CP than a clinical assessment alone (Novak et al., 2017). In countries where the MRI is not available or affordable, the HINE is recommended for early diagnosis of CP (Novak et al., 2017).

#### 2.2.2.2 Developmental coordination disorder

In children born very preterm without CP, mild to moderate motor impairments consistent with developmental coordination disorder (DCD) may occur. DCD is defined as impaired motor skills that 1) are far below the expected level for age, 2) interfere with academic achievement or activities of daily living, 3) are present at an early age, and 3) cannot be explained by other medical, neurological or cognitive impairments (Blank et al., 2019). In clinical setting, the diagnosis of DCD requires that the children meet specific criteria according to the DSM-V or ICD-10 (Blank et al., 2019). In study settings, mild and moderate motor impairments analogous to DCD, are often referred to with a various terminology including e.g. probable DCD, at risk for DCD, non-CP motor impairment and motor impairment other than CP.

The prevalence of DCD is estimated to range from 5% to 6% in the general pediatric population and from 8% to 37% in children born preterm and/or with low birth weight (Blank et al., 2019; Bolk et al., 2018; Griffiths et al., 2017; Howe et al., 2011; Setänen et al., 2016; Williams et al., 2010). An increase in the rate of motor impairment other than CP has been reported in children born extremely preterm (Spittle et al., 2018).

The etiology of DCD is most likely multifactorial. There is limited data available for the early risk factors for DCD and only preterm birth and male sex have been consistently associated with an increased risk of DCD (Van Hoorn et al., 2021). There is some evidence of the association between abnormal brain MRI findings at term and later DCD (Van Hoorn et al., 2021). Brain imaging studies of children with DCD have shown alterations in the brain structure and function compared with typically developing peers (Brown-Lum & Zwicker, 2015; Wilson et al., 2017). It has been suggested that especially the cerebellum and basal ganglia are linked to DCD, and that alterations in the cerebellum and basal ganglia may indicate susceptibility to neurodevelopmental difficulties in general, not only to DCD (Biotteau et al., 2016). In children with DCD, other developmental difficulties, such as specific language impairment, mathematical problems and learning disorders, are often present (Blank et al., 2019). Thus, it seems reasonable that brain MRI alterations observed in children with DCD are not exclusive to DCD but may overlap with other developmental impairments.

A standardized motor assessment method should be used to identify children with DCD. Questionnaires evaluating the motor outcome, such as Developmental Coordination Disorder Questionnaire 2007 (DCDQ ’07) (Wilson et al., 2009), can be used to support the motor assessment and the identification of children at risk for DCD. The criteria of DCD emphasize that the signs of motor impairment should be present in early childhood. However, the diagnosis of DCD is not generally recommended before 5 years of age as spontaneous catch up of delayed motor development may occur in young children. In addition, the cooperation, motivation and acquisition of skills required in activities of daily living may fluctuate. Data on the stability of DCD diagnosed at an early age is limited. (Blank et al., 2019.)

DCD has been shown to co-occur with other developmental disorders. It has been reported that the co-occurence rate of DCD with attention-deficit/hyperactivity disorder (ADHD) is at least 50%, with adverse language skills up to 70%, and with behavioral problems around 40%. (Blank et al., 2019; Bolk et al., 2018). Many children with DCD have an indication for intervention due to the adverse effect of DCD on their activities of daily living. Intervention should be targeted on the problem with the most severe impact on functioning, activity, and participation. Activity-orientated/participation-orientated approaches with individually set goals are recommended (Blank et al., 2019).

#### 2.2.2.3 Minor neurological dysfunction

Minor neurological dysfunction (MND) can be classified as simple MND or complex MND. Simple MND means typical but non-optimal brain function with limited clinical significance, e.g. the combination of mild hypotonia and exaggerated tendon

reflexes. Complex MND has been proposed to associate with structural brain deficit and suggested to be considered as a borderline form of CP. It denotes dysfunctions in three or more neurological domains, e.g. coordination, fine manipulation, posture and muscle tone, and reflex activity. (Hadders-Algra, 2002.) During the past decades, the rate of simple MND has increased from 15% to 20%, while the rate of complex MND has remained stable at 6–7% in the general population (Hadders-Algra, 2010). The reported rate of simple MND in children born extremely or very preterm ranges from 29% to 42% and the rate of complex MND from 8% to 11% at 6 years and 11 years of age (Broström et al., 2018; Setänen et al., 2016). Decreasing gestational age and postnatal corticosteroid therapy have been shown to associate with an increased risk of MND in children born very preterm (Arnaud et al., 2007). Structural brain abnormalities, e.g. grade III intraventricular hemorrhage and white matter abnormalities, on neonatal ultrasonography or MRI have been linked with an increased risk for subsequent complex MND (Arnaud et al., 2007; Barnett et al., 2002).

Children with MND can be identified with a standardized and age-adequate neurological examination (Ferrari et al., 2012). The Touwen Infant Neurological Examination can detect early signs of MND already at 18 months of age (Hadders-Algra et al., 2010). However, the signs and presence of MND may fluctuate during childhood and adolescence, and an instability of neurological condition in infancy and early childhood has been described especially in children born preterm (Hadders-Algra, 2002, 2010). Thus, it has remained a challenge to detect those young children at risk for a subsequent complex MND.

MND, particularly complex MND, has shown to associate with concurrent motor, cognitive and behavioral problems (Broström et al., 2018; Hadders-Algra, 2010; Kikkert et al., 2013). Moreover, complex MND is more common in school-age children attending special education compared to those in mainstream education (Peters et al., 2011). Possible interventions for children with MND are less studied compared to interventions for CP or DCD. It has been suggested that identification of MND and its distinction into simple and complex form supports the selection of an optimal therapeutic approach (Hadders-Algra, 2010).

#### 2.2.2.4 Fine motor skills

Fine motor skills denote the coordination of small muscles, for example of the hands and fingers, with vision. Fine motor skills are essential in various daily activities such as manipulating objects, drawing and writing, eating, dressing, washing and brushing teeth. Caramia et al. (2020) have shown that school-aged children spent 37% to 60% of the school day performing fine motor activities. Children born very preterm have shown to have poorer fine motor skills compared to general population

(De Kieviet et al., 2009). In children born very preterm, the reported rate of fine motor impairment (defined as as <15th percentile on standardized tests, e.g. the Movement Assessment Battery for Children) is up to 40%, whereas the rate of fine motor impairments in school-aged children in general is 7% (defined according to the domain of Fine manipulative ability of the Touwen Neurological Examination) (Bos et al., 2013; Hadders-Algra, 2010). Longitudinal data has indicated that in children born with very low birth weight (≤1500g) impairments in fine motor skills persist into early adulthood (Husby et al., 2013). Impairments in fine motor skills might have negative effect on school performance and academic achievement as well as on leisure activities, social participation and performance of daily tasks in children and young adults born preterm/very low birth weight (Bos et al., 2013; Husby et al., 2013).

### 2.2.3 Cognitive outcome

Very preterm birth increases risk for different levels of cognitive impairment (Brydges et al., 2018; Hirvonen et al., 2017; Pascal et al., 2018). A systematic review reported that the prevalence rate of moderate-to-severe cognitive delay (<-2 SD) in children born very preterm at 8–36 months of age is 8.2%, and up to 14.7% at 2–5 years of age (Pascal et al., 2018). Although the general cognitive outcome of 11 year-old children born very preterm is in the average range, it is lower than the mean outcome of the norm population (Nyman et al., 2017).

Etiology of cognitive impairment is multi-factorial. The degree of prematurity affects the cognitive outcome especially during the first years of life (Brydges et al., 2018; Linsell et al., 2015). In some studies, major brain pathology in MRI at term is a risk factor for poorer cognitive outcome (Nyman et al., 2017) while in others the prognostic value of neonatal brain MRI findings on long-term cognitive development has been less significant (Linsell et al., 2015). A low level of paternal education is a risk factor for a poorer cognitive outcome in children born very preterm even after 5 years of age, whereas a higher parental (especially paternal) education seems to be a protective factor of a better cognitive outcome (Linsell et al., 2015; Nyman et al., 2017). The influence of environmental and social risk factors on cognitive outcome is suggested to become more pronounced with age (Linsell et al., 2015).

Structured neurological examination before or at 12 months of corrected age has shown to predict the cognitive outcome at 2 years of corrected age in children with and without CP and irrespective of the gestational age (Romeo et al., 2020, 2022). A stability of cognitive outcome from 2 years to 5 years and from 5 years to 11 years has been described in children born very preterm (Munck et al., 2010; Nyman et al., 2017).

### 2.2.4 Neurodevelopmental follow-up

To identify possible problems, enhanced surveillance until 2 years of corrected age is recommended for all children born <30 weeks of gestation and for children born preterm (<37 weeks of gestation) with brain lesion likely to be associated with developmental problems, grade II or III hypoxic ischaemic encephalopathy, or neonatal bacterial meningitis. The follow-up visits should include evaluation of e.g. neurological, cognitive and behavioral development. Assessments of developmental outcomes, including for instance cognitive development, are recommended for children born <28 weeks of gestation at 4 years of age. At school age, it is important that both the carers and teachers are aware that preterm birth may have long-lasting effects on several aspects of development, thus affecting for instance the child's academic abilities and mental health. (EFCNI, 2018; National Guideline Alliance (UK), 2017.)

### 2.2.5 Assessment methods

Neurodevelopment should be assessed by using a structured, standardized method. In children born very preterm, the gestational age status should be taken into account until 2 years of corrected age when applying the age specific norms.

The Prechtl's Assessment of General Movements (GMA) is a standardized method for assessing the spontaneous movements of infants from preterm age to 20 weeks of corrected age. In this method, the general movements are assessed from video recordings. The general movements are commonly referred to as writhing movements until 2 months of corrected age after which they change to fidgety movements that are present in an awake infant at 3 to 5 months. (Einspieler & Prechtl, 2005). The sensitivity and specificity of GMA for CP were 98% and 91%, respectively (Bosanquet et al., 2013). Abnormal general movements may also indicate a risk for subsequent cognitive impairment (Einspieler et al., 2016).

The Hammersmith Neonatal Neurological Examination is a standardized examination for infants born extremely preterm to full term. It includes assessment of tone, tone patterns, reflexes, movements, abnormal signs, and behavior; these can be scored and summed up to form a global score. Infants born preterm should be assessed according to normative data of gestational age categories due to differences in neurological examination between infants born preterm and full-term (Mercuri et al., 2003; Ricci et al., 2008).

The Standardized Infant NeuroDevelopmental Assessment (SINDA) is a relatively recently published method for preterm and full-term infants aged 6 weeks to 12 months (Hadders-Algra et al., 2019). It has three scales: a neurological scale, a developmental scale and a socio-emotional scale. The neurological scale includes assessment of spontaneous movements, cranial nerve function, motor reactions,

muscle tone, and reflexes; with a special focus on the quality of spontaneous motility. The SINDA has reportedly shown a promising ability to predict adverse cognitive development and CP at 24 months of age.

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) is a widely used assessment method for early development of preterm and full-term infants from 1 to 42 months of age (Bayley, 2005). It includes multiple developmental domains: fine and gross motor, cognition, language and social-emotional, and adaptive behavior. Motor, cognitive and language scales can also be administered independently. Motor scale consists of fine motor section including 66 items and gross motor section including 72 items. Bayley-III conducted at 2 years has shown to have sensitivity of 7% and specificity of 94% for motor delay (≤15th percentile in standardized motor test) at 4 years (Burakevych et al., 2017).

The HINE (Haataja et al., 1999) is widely used in developmental follow-up of children born preterm. Its neurologic examination comprises scorable assessments of cranial nerve function, posture, movements, tone, and reflexes. Moreover, it includes non-scorable assessments of developmental milestones and behavior. Standardized norms for full-term infants between 12 and 18 months of age have been published (Haataja et al., 1999). The reported sensitivity and specificity of the HINE at 3 months for later CP are both 90% (Romeo et al., 2016) and the HINE has shown to correlate with the functional level (e.g. ambulation) of the CP (Romeo et al., 2008). Higher HINE scores have been shown to correlate with better cognitive outcome in children born preterm and at term (Romeo et al., 2020, 2022).

The Movement Assessment Battery for Children – Second Edition (Movement ABC-2) is a common method to evaluate a child's motor development and to identify DCD (Blank et al., 2019; Henderson & Sugden, 1992; Henderson et al., 2007). The subscales of the Movement ABC-2 are manual dexterity (three tasks), aiming and catching (two tasks), and balance (three tasks); the specific tasks in the subscales depend on the age band. The Movement ABC-2 at 4 years has been shown to have sensitivity of 79% and specificity of 93% for predicting motor impairment (≤5th percentile in Movement ABC-2) at 8 years. (Griffiths et al., 2017). The norms are provided in the manual, but since the norms have been shown to vary between populations it is recommended to adapt the norms to different countries (Blank et al., 2019).

The Bruininks-Oseretsky Test of Motor Proficiency-2 assesses motor skills and DCD from 4 to 21 years of age (Blank et al., 2019; Bruininks & Bruininks, 2005). The test has eight subtests: fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed and agility, upper-limb coordination, and strength. A composite score for fine motor and gross motor parts can be administered separately or the scores can be summed up to obtain composite core of general motor proficiency. Studies have reported varying results of test-retest

reliability of the Bruininks-Oseretsky Test of Motor Proficiency-2 (Blank et al., 2019; Griffiths et al., 2018). Age-based American and German norms are available (Blank et al., 2019).

Peabody Developmental Motor Scales-2 is a standardized and validated method to evaluate gross motor and fine motor skills of 0–5-year-old children. The fine motor scale of the Peabody Developmental Motor Scales-2 consists of two subtests measuring grasping and visual-motor integration. The test evaluates both qualitative and quantitative characteristics of the motor skills. (Folio & Fewel, 2000.)

The Touwen examination is designed to detect MND from 4 years of age. The comprehensive, age-specific neurological examination includes assessment of eight domains: posture and muscle tone, reflexes, fine manipulation, involuntary movements, associated movements, coordination and balance, sensory function, and cranial nerve function. Based on the numbers of dysfunctional domains and the type of dysfunction, the neurological outcome is classified into neurologically typical, simple MND or complex MND. (Hadders-Algra, 2010.)

The Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV), is a standardized method to assess cognitive outcome. It is suitable from for children and adolescents 6 to 16 years of age. General intelligence is measured with a full-scale IQ, which consists of the Verbal Comprehension Index, the Perceptual Reasoning Index, the Working Memory Index, and the Processing Speed Index. The classification is based on the manual, and Finnish norms are available. The standardization sample of the Finnish edition of the WISC–IV consists of 940 children and adolescents between the ages of 6 and 16 years. (Wechsler, 2011a, 2011b.)

## 2.3 Health-related quality of life

Health-related quality of life (HRQoL) is an individual's or a group's perceived physical and mental health over time (CDC, 2021). It is a useful measure to assess the effect of neonatal morbidities and developmental difficulties, because it combines physical health with psychological and social well-being in one outcome measure (Theunissen et al., 2001). The presence of prematurity-related morbidity such as CP, hearing or visual impairment, epilepsy, obstructive airway disease, ADHD, or severe cognitive impairment has been shown to associate with lower self-experienced HRQoL in 8-year-old children born very preterm (Huhtala et al., 2016). Consistently, another study reported that surgical closure of patent ductus arteriosus, ADHD, and severe neurodevelopment impairment were predictors of poorer HRQoL in 12-year-old children born very preterm (Natalucci et al., 2017). However, these studies also reported that the majority of the children born very preterm experienced an HRQoL equal to their peers (Huhtala et al., 2016; Natalucci et al., 2017).

It has been suggested that the impact of premature birth diminishes from childhood to adulthood (Zwicker & Harris, 2008), and it has been shown that adults born preterm have reported HRQoL similar to controls born at term (Björkqvist et al., 2018). However, a recent study assessing HRQoL of individuals born preterm born with a birth weight ≤ 1500 g and controls born at term, showed that those born preterm reported lower HRQoL at 32 years compared to controls. Moreover, HRQoL of individuals born preterm was shown to decline from 20 to 32 years of age. (Berdal et al., 2022.)

Most studies regarding the HRQoL of preschool-aged children are based on parent-reported measures. It has been suggested that parents of the children born very/extremely preterm perceive their child's HRQoL lower than the parents of children born full-term although the children themselves did not (Zwicker & Harris, 2008). The agreement regarding the HRQoL between adolescents and their parents has shown to depend on the domain of health attributes, and higher agreement has been reported in observable and physical domains and lower agreement in more psychological domains, such as cognition, emotion and pain (Wolke et al., 2013).

The 17-Dimensional Illustrated Questionnaire (17D) includes 17 multiple-choice questions of health and function for children aged from 8 to 11 years (Apajasalo et al., 1996). The 17D questionnaire can be self-administered or completed by structured interview. It is available in English, Finnish, French and Swedish. The questions concern mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends, and concentration. Each question has a five-level tick box functioning scale alternating from a perfect level to a severe dysfunction. The overall HRQoL score is calculated from the health state descriptive system using population-based preference or utility weights for 11-year-old healthy Finnish school children. The overall score varies from 0 (worst, equal to death) to 1 (best, equal to complete health). For adolescents aged at 12 to 15 years, the 16D questionnaire with similar principles can be administered (Apajasalo et al., 1996).

The KIDSCREEN-52 (long version) and the KIDSCREEN-27 (short version) are questionnaires for assessing the subjective health and well-being of children and adolescents aged from 8 to 18 years (Ravens-Sieberer et al., 2007, 2008). To ensure cross-cultural validity, the KIDSCREEN has been simultaneously developed in 13 European countries (Ravens-Sieberer et al., 2008). The self-report or proxy-administered measures are applicable for healthy and chronically ill children. The KIDSCREEN-27 has five domains that include physical well-being, psychological well-being, autonomy and parents, peers and social support, and school environment. In addition to these five domains, the KIDSCREEN-52 also includes the domains of moods and emotions, self-perception, parent relations and home life, social

acceptance (bullying), and financial resources. Each domain is scored on a 5-point scale, and the scores yield dimensions of HRQoL.

## 2.4 Brain magnetic resonance imaging

### 2.4.1 Neonatal magnetic resonance imaging

The neonatal brain MRI has shown to provide information about the structure of the developing brain and to detect brain injury and altered brain development in newborns (Anderson et al., 2015). In high-income countries where MRI is available, brain MRI at term age has become a routine procedure in children born very/extremely preterm. Major pathologies in neonatal brain MRI can help to identify neonates with an increased risk for CP (Novak et al., 2017) while normal MRI findings have shown to have a high negative predictive value for CP and subsequent cognitive impairment (Setänen et al., 2013). White matter abnormalities in neonatal structural brain MRI have shown to associate with subsequent motor impairment even in the absence of CP in children born very preterm (Spittle et al., 2011). It has been shown that the neonatal brain MRI volumes of precentral gyrus, cerebellum, and brainstem correlated positively with fine motor skills at 6 years, whereas a negative correlation between the cortical grey matter volume and fine motor skills was shown in children born extremely preterm (Bolk, et al., 2018). The MRI findings should always be interpreted as an adjunct to the clinical information on the child. It has very recently been also shown, that there are even connectome-level differences between brains of preterm and term-born infants using structural and diffusion MRI sensitized for neuronal pathways (Blesa et al., 2021).

### 2.4.2 Functional magnetic resonance imaging

To assess the differences in neural activation and brain functioning, a functional MRI (fMRI) can be used. The fMRI demonstrates regional, time-varying activation of the brain. In short, when a brain region is activated by a task, such as finger movement, the increased signaling processes cause a locally increased energy requirement. The transient consumption of local oxygen stores in tissues close to capillaries leads to a vasomotor reaction. This causes a dilation of these vessels resulting in an increased blood flow that exceeds the local neuronal oxygen demand. Thus, task induced brain activation results in surplus of oxygenated hemoglobin and a relative decrease in deoxygenated hemoglobin. During resting states this condition returns to normal. This alteration in local cerebral blood flow and changes in activation can be detected by MRI, because deoxygenated hemoglobin is significantly paramagnetic and causes a decrease in the measured MRI signal during resting state. This is also called BOLD

(blood oxygenation level dependent) MRI contrast. Typically, fMRI experiments use e.g. visual or auditory stimuli to induce two states in the subject while continuously collecting MRI volumes. For example, a block design, i.e. task-rest-task-rest etc, can be used to assess the alternation of brain activation between the experimental and control conditions. (Glover, 2011.)

Fine motor tasks, such as finger tapping, have been commonly used in fMRI studies to evaluate the function of the motor system. A meta-analysis of finger-tapping fMRI studies in adults have shown that the regions commonly associated with the tasks were the primary sensorimotor cortex, supplementary motor area, basal ganglia, and anterior cerebellum, regardless of the complexity of the tapping task (Witt et al., 2008). The brain activation during finger tapping has shown to depend on the task complexity and pacing stimuli, as single-finger tasks seemed to cause only contralateral activation whereas unimanual multi-finger tasks and bimanual tasks evoked bilateral activation (Witt et al., 2008). However, findings from the studies with adult participants cannot be generalized to the pediatric population since children, compared to adults, have shown to exhibit different activation during motor tasks regarding both the activation levels and the areas activated (De Guio et al., 2012; Turesky et al., 2018).

It has been suggested that children with DCD, compared with peers without DCD, demonstrate different brain activation during motor tasks and that particularly cerebellum and basal ganglia associate with DCD (Biotteau et al., 2016; Wilson et al., 2017). However, very limited data is available on brain activation findings in children born very preterm with or without DCD. Although very preterm birth has shown to increase the risk for DCD (Blank et al., 2019), very preterm birth also seems to affect the brain functioning during motor tasks in children born very preterm without DCD. An fMRI study by Lawrence et al. (2014) has shown that 20-year-olds born very preterm without DCD displayed greater activation in right cerebellum, extending into the lingual, parahippocampal and middle temporal gyri during the motor task of the right hand compared to peers born at term.

# 3 Aims

The objective of this thesis was to study the long-term neurodevelopmental outcome and brain fMRI findings in children born very preterm. The specific aims of the three publications are presented below.

In Study I, the aim was to study the rate of DCD and to evaluate the association between motor and cognitive outcome in a cohort of 11-year-old children born very preterm. Another aim was to study the impact of DCD on concurrent self-experienced HRQoL.

In Study II, the aim was to study the association between neurological examination at 2 years of corrected age and the neurodevelopment i.e. neurological, motor and cognitive outcomes at 11 years of age in children born very preterm. Another aim was to study the association between the concurrent neurological and cognitive outcomes at 11 years of age.

In Study III, the aim was to study the hand coordination skills of 13-year-old adolescents born very preterm and controls born full-term. Another aim was to study the brain activation in fMRI during these hand coordination tasks between the groups of adolescents born very preterm and full-term.

# 4 Materials and Methods

## 4.1 Participants

### 4.1.1 Children born very preterm

This prospective study is part of the PIPARI (Pienipainoisten riskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään; The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) study of infants born very preterm. The participants were born to Finnish or Swedish speaking families from January 2001 to December 2006 in Turku University Hospital. From 2001 to 2003 the inclusion criteria were birth weight ≤1500 grams and prematurity (<37 gestational weeks). From 2004, the inclusion criteria were amended to all infants born <32 weeks of gestational age irrespective of birth weight. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting development.

In Studies I and II, children born very preterm from 2001 to 2006 were included. In Study III, children born very preterm from April 2004 to December 2006 were included; this was because from April 2004 onwards upgraded MRI equipment was used for the neonatal brain MRI at term. In Study III, the children with severe cognitive impairment (full-scale intelligence quotient <70), CP, severe hearing and/or visual impairment, and children with major brain pathology at 13 years were excluded.

### 4.1.2 Controls born full-term

The control group included healthy children born full-term in Turku University Hospital from 2003 to 2004. These children were recruited by inviting the parents of the first boy and the first girl born on each week to participate in the study. If the family refused, the parents of the next boy and girl were invited. The controls were born ≥37 weeks of gestation and were not admitted to a neonatal care unit during the first week of life. At least one of the parents had to speak either Finnish or Swedish. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting development, the mother's use of illicit drugs or alcohol during pregnancy,

and the child's small for gestational age status. The control group was included in Study III.

## 4.2 Methods

The study design of this thesis is shown in Figure 1. Corrected age was applied until 2 years after which the calendar age was used.

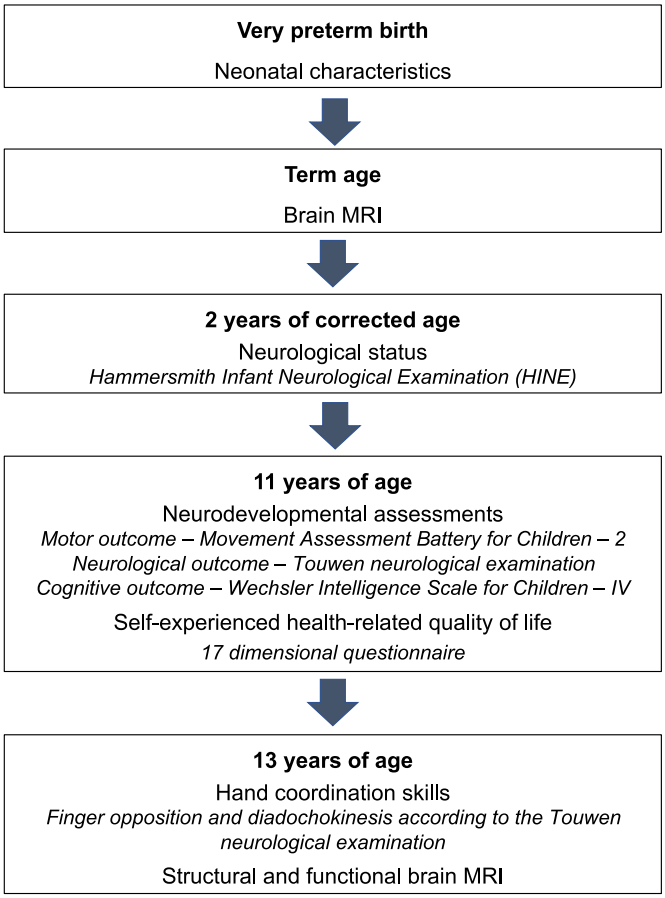



**Figure 1.** Study design of the thesis.

### 4.2.1 Background data

Neonatal background data was acquired from the medical records using the Vermont-Oxford Network criteria. The neonatal characteristics were gestational age, birth weight, small for gestational age status (<-2 SD), gender, cesarean delivery, bronchopulmonary dysplasia (supplemental oxygen required at 36

weeks of postmenstrual age), operated necrotizing enterocolitis, sepsis, and laser-treated retinopathy of prematurity. The background data also included the brain MRI findings at term age (4.2.2). The levels of parents' education, including both mother's and father's education, were included since it has been shown that lower levels of parental education associate with an increased risk for an adverse cognitive outcome (Linsell et al., 2015). The parents' education was categorized as ≤12 years of education (including parents with ≤9 years of basic education and those with upper secondary education) or >12 years of education (parents with higher education) or >12 years of education (parents with higher education).

### 4.2.2 Neonatal brain magnetic resonance imaging

All infants born very preterm underwent a brain MRI at term. The imaging was conducted during postprandial sleep without any pharmacological sedation or anesthesia. The infants were swaddled to reduce movement artifacts and to calm them during the examination. A pulse oximeter and ear protection (3M Disposable Ear Plugs 1100; 3M, Brazil and Wurth Hearing protector, Art.-Nr. 899 300 232, Wurth, Austria) were routinely used during the imaging.

For infants born between January 2001 and April 2004, the MRI equipment was an open 0.23-T Outlook GP (Philips Medical, INC, Vantaa, Finland), after which it was upgraded to the 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands) and used for the rest of the study infants. When the 0.23-T equipment was used, axial T2-weighted images, coronal three-dimensional T1-weighted images and coronal T2-weighted images of the entire brain were obtained. With the upgraded 1.5-T equipment, axial T2-weighted, axial T1-weighted, and sagittal T2-weighted images were obtained. All of the sequences were optimized for the imaging of a term infant brain. The total imaging time was about 25 minutes.

The neonatal brain MRI data was evaluated by one neuroradiologist (R.P.) who was unaware of the clinical information of the child. The brain MRI findings were classified into three groups: normal findings, minor pathologies, and major pathologies. The classification criteria are shown in Table 1. The width of the extracerebral space was measured at the front of the frontal lobe, where the extracerebral fluid space is widest. A cut-off value of 4 mm was used according to a previous study (McArdle et al., 1987). Ventricular/brain ratio was obtained from the width of the frontal horns of the lateral ventricles divided by the width of the brain tissue at the same plane of cerebral image.

**Table 1.** The classification of the neonatal brain MRI performed at term. (Modified from Setänen et al., 2013)

| | |
|---|---|
| Normal findings | • Normal anatomy of the cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures<br>• Extracerebral space width <5 mm<br>• Ventricular/brain ratio <0.35 |
| Minor pathologies | • consequences of intraventricular hemorrhages grade I or II<br>• caudothalamic cysts<br>• Extracerebral space width of 5 mm<br>• Ventricular/brain ratio of 0.35 |
| Major pathologies | • Consequences of intraventricular hemorrhages grades grades III or IV<br>• Injuries in cortex, basal ganglia, thalamus or internal capsule, corpus callosum, cerebellum or white matter<br>• Extracerebral space width >5 mm<br>• Ventricular/brain ratio >0.35<br>• Other major brain pathology (infarcts) |

### 4.2.3 Hammersmith Infant Neurological Examination (HINE)

The neurological status of the study children born very preterm was assessed by trained physician and physiotherapist using the HINE at 2 years of corrected age (Haataja et al., 1999). It consisted of three sections: neurologic examination, assessment of developmental milestones, and assessment of behavior. The neurologic examination included 26 items evaluating five subsections: cranial nerve function, posture, movements, tone and reflexes. The assessment of developmental milestones included eight items describing motor functions, and the assessment of behavior included three items evaluating behavior. The items of the first section were scored individually and these item scores were summed up to calculate the subsection scores and the global score (minimum 0, maximum 78).

The diagnosis of CP was confirmed after a systematic clinical follow-up at 2 years of corrected age by an experienced child neurologist. The Gross Motor Function Classification System (GMFCS) was used to classify the severity of CP (Palisano et al., 1997).

### 4.2.4 Movement Assessment Battery for Children – 2

The motor outcome at 11 years of age was evaluated with the Movement ABC-2 (Henderson & Sugden, 1992; Henderson et al., 2007) by the author or one of the two fellow physicians. The raw scores were converted into total standard scores and percentile scores according to the test manual, using age band 3 (11 to 16 years) and the norms for 11-year-old children. A total test score >15th percentile indicated normal motor outcome, >5th to 15th percentile indicated risk of movement difficulties, and ≤5th percentile denoted DCD. The Movement ABC-2 examinations were video recorded to enable reassessment and to guarantee the comparability between examinations.

### 4.2.5 Touwen neurological examination

The neurological outcome at 11 years of age was assessed with the latest complete version of the Touwen neurological examination. The examination includes assessment of eight domains: posture and muscle tone, reflexes, fine manipulation, involuntary movements, associated movements, coordination and balance, sensory function, and cranial nerve function (Hadders-Algra, 2010). It was performed by one of the three physicians who also performed the Movement ABC-2 except for the ophthalmological part, which was assessed by one ophthalmologist as a part of comprehensive ophthalmological assessment (Lehtonen et al., 2022). The examinations were classified according to the classification criteria of Hadders-Algra using computerized scoring (Hadders-Algra, 2010). The outcome was neurologically typical if the child had no abnormal domains, simple MND if the child had one or two dysfunctional domains and complex MND if more than two domains were dysfunctional. According to the manual, an isolated presence of dysfunction in the domain of reflexes did not qualify for the classification of simple MND (Hadders-Algra, 2010). Children with an outcome of neurologically typical or simple MND were classified as having a typical neurological outcome. This classification was done to highlight the clinically important features of complex MND (Hadders-Algra, 2002). All the Touwen examinations were video recorded and, in cases where there was of any hesitation regarding the examinations, the videos were reassessed with an experienced child neurologist.

### 4.2.6 Wechsler Intelligence Scale for Children – IV

The cognitive outcome was assessed with a Finnish translation of the WISC-IV, at 11 years of age (Wechsler, 2011a, 2011b). The assessment was performed either in Finnish or Swedish according to child's native language. Finnish assessments were performed by one of the two Finnish-speaking psychologists and Swedish

assessments by a native Swedish-speaking psychologist. General intelligence was measured with a full-scale IQ, which consists of four indexes: verbal comprehension, perceptual reasoning, working memory and processing speed. The classification was based on the test manual (Wechsler, 2011a, 2011b). The scores were classified as average if the full-scale IQ was ≥90, low average 80–89, and borderline 70–79; moreover, a full-scale IQ≥70 was classified as normal cognitive outcome. A full-scale IQ <70 (<-2 SD) was classified as severe cognitive impairment.

### 4.2.7 Self-experienced health-related quality of life

The self-experienced HRQoL was evaluated using the 17D questionnaire at 11 years of age (Apajasalo et al., 1996). The domains of the 17D include mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, school and hobbies, learning and memory, discomfort and symptoms, depression, distress, vitality, appearance, friends, and concentration. Each of the 17 domains has a five-level tick box functioning scale alternating from a perfect level to a severe dysfunction. The children completed the questionnaire by themselves or, if the child was not able to read, as an interview by the physician before the motor and neurological assessments. The relative weights of each dimension were defined in the instrument's home page (Apajasalo et al., n.d.). The 17D overall score i.e. HRQoL was calculated from the health state descriptive system using population-based preference or utility weights for 11-year-old healthy Finnish school children. The HRQoL score varied from 0 (worst score, equal to death) to 1 (best score, equal complete health) (Apajasalo et al., 1996).

### 4.2.8 Hand coordination skills

At 13 years of age, hand coordination skills, including finger opposition and diadochokinesis, of adolescents born very preterm and controls born full-term were assessed according to the Touwen neurological examination (Hadders-Algra, 2010) by the author or one of the two fellow physicians. Only right-handed adolescents were included to minimize the effect of handedness. In the finger opposition, the participants were asked to place the fingers of one hand, starting with index finger, repeatedly on the thumb of the same hand in the following sequence: 2, 3, 4, 5, 4, 3, 2, 3, 4, 5, etc while keeping the other arm relaxed at their side. In the diadochokinesis, the adolescents were asked to hold one arm at an angle of 90º at the elbow, the hand pointing forward, and to quickly perform a pronation-supination of the hand and forearm while keeping the other arm relaxed at their side. The performance of each task was scored separately for each hand according to the classification criteria of

the Touwen neurological examination manual using the norms for 13-year-olds. All the assessments were video recorded and reassessed together with an experienced child neurologist. This was done to guarantee the analogy within the classifications. The scoring of hand coordination tasks was performed based on the assessments outside the scanner before the fMRI. During in-scanner hand coordination tasks, the accomplishment of the hand coordination task was observed, but the performance was not repeatedly scored.

### 4.2.9 Brain magnetic resonance imaging at 13 years

At 13 years of age, structural and functional brain MRI was performed on both adolescents born very preterm and controls born full-term. The equipment was 3T Philips Ingenuity TF PET/MR (Philips, Amsterdam, Netherlands) with a SENSE Head-32-channel coil. Ear protection (3M disposable ear plugs, São Paolo, Brazil and hearing protection, Wurth, Austria) was used. During the imaging, the adolescents were asked to lie on their back with their eyes open and gaze at the central cross shown on an adjustable binocular system, VisualSystem (NordicNeuroLab). If the adolescent had fixed orthodontic appliances, it was removed and replaced by a dentist during the scanning visit; this was for patient security and to minimize ferromagnetism-related artifacts.

#### 4.2.9.1 Structural magnetic resonance imaging

The MRI assement started with structural scans: sagittal T1-weighted images, axial T2-weighted images, and coronal sagittal images. The structural MRI were evaluated by the same experienced neuroradiologist, blinded for the previous clinical and imaging data, who had assessed the neonatal brain MRI of the participants born very preterm at term. The brain MRI findings at 13 years were classified into three groups: normal findings, minor pathologies, and major pathologies. The classification criteria are shown in Table 2.

**Table 2.** The classification of the structural brain MRI performed at 13 years of age.

| | |
|---|---|
| Normal findings | • Normal brain signal intensity<br>• Normal anatomy of the cortex and cortical gyration pattern, basal ganglia and thalami, internal and external capsule, white matter, corpus callosum, cerebellum, pons and medulla oblongata<br>• Normal cerebrospinal fluid spaces |
| Minor pathologies | • Mild prominence of one of the four lateral ventricular horns without brain parenchyma pathologies<br>• Minor punctuate cerebral white matter T1 hyperintensity |
| Major pathologies | • Consequences of intraventricular hemorrhages grades grades III or IV<br>• T2 hyperintensity of the cerebral or cerebellar parenchyma corresponding to focal hemosiderin collection<br>• Symmetric or asymmetric white matter damage corresponding to white matter gliosis<br>• Marked dilatation of the ventricles or marked dilatation of the cortical cerebrospinal fluid spaces<br>• Signs of infarcts or cystic, and/or hemorrhagic white or greymatter damage |

#### 4.2.9.2 Functional magnetic resonance imaging

The BOLD data for the entire brain volume (35 axial slices of 4 mm thickness) were gathered using a single-shot sequence for T2*-weighted echo planar imaging with 2.0s TR, 20ms TE, 75° flip angle, 80×80 matrix, and 3mm in-plane resolution. Each of the four fMRI runs consisted of 80 scans including the first 4 dummy scans to allow for T1 equilibration. Visual stimulus delivery during the fMRI sessions was controlled by the Presentation software (Neurobehavioral Systems, Inc., Albany CA, USA).

During the fMRI, adolescents performed the same self-paced, unimanual hand coordination tasks as during the out-of-scanner performance assessment. The instructions were explained before entering the fMRI scanner and repeated orally before each task run by the same physician who had performed the clinical examination of the hand coordination tasks. There were four runs: 1) finger opposition of the right hand, 2) finger opposition of the left hand, 3) diadochokinesis of the right hand, and 4) diadochokinesis of the left hand. Each fMRI run consisted of 4 sets, each set tasks included 19s of gaze fixation followed by 19s of hand coordination task. The fMRI protocol is shown in Figure 2. Alternation of the hand coordination task and gaze fixation was guided visually by presenting a hand image for the task periods and a central cross for the gaze fixation periods. During the gaze fixation periods, participants were asked to keep their hand still and eyes on the

fixation cross. The participants were able to stop the scan and to communicate with the physician using an in-scanner intercom by squeezing a ball on their stomach at any time.

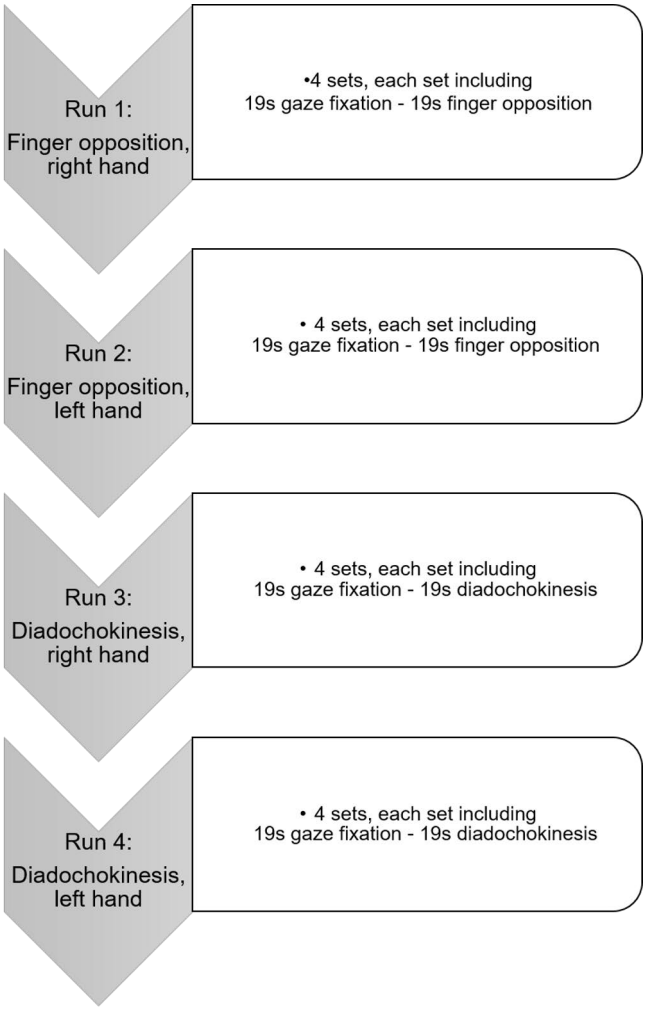



**Figure 2.** The functional magnetic resonance imaging protocol at 13 years of age.

A composite region of interest (ROI) was built to perform the analysis. The neural activation during hand coordination tasks was evaluated within a ROI represented by a set of cortical and cerebellar regions known to relate to sensorimotor activity of the wrist and fingers. A cortical part of the composite ROI included regions used in the studies of the neural basis of multi-finger sequences (Wiestler et al., 2011; Yokoi et al., 2018): bilateral primary sensory cortex, primary motor cortex,

dorsal premotor cortex, medial premotor cortex, and superior parietal lobule. The Human Motor Area Template (Mayka et al., 2006) was used to define the S1, M1, and premotor regions, the "Neuromorphometrics" Atlas available in the CAT12 software and based on data from the OASIS project (http://www.oasis-brains.org/) and the Neuromorphometrics, Inc. (http://neuromorphometrics.com/) was used to define the superior parietal lobule. Only a dorsolateral part of the primary sensorimotor cortex in the range of z coordinate from +40 to +75 was included in the composite ROI. This was done so as to reliably cover representations of the digits and wrist while minimizing the influence of the signal from irrelevant body parts like the mouth, trunk and legs (Roux et al., 2018; Roux et al., 2020). The cerebellar lobules V, VI, VIII, and Cruse I were included since they are the ones most strongly associated with sensorimotor hand and finger representation according to studies on cerebellar somatotopy (Boillat et al., 2020; van der Zwaag et al., 2013; Wiestler et al., 2011). To define the cerebellar areas, the Spatially Unbiased Infratentorial Template was used (Diedrichsen, 2006). All the regions were combined into one and masked with the grey matter mask. The total volume of the resulting ROI was 9218 3-mm cubic voxels.

To process the fMRI data, the Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (MathWorks Inc., Natick MA, USA) was used. The fMRI data were corrected for head motion within each subject in a two-pass realignment procedure. The slice-timing difference was corrected by temporal interpolation using the acquisition time of the middle slice as a reference. For each subject, functional data were co-registered with the T1-weighted image. The T1-weighted images were used to create a group structural brain template and a gray matter mask. Considering the potential systematic structural differences between the brains of the 13-year-olds and adults, a customized group-specific structural brain template was created with the Computational Anatomy Toolbox, CAT12 (Gaser & Dahnke, 2016); Template-O-Matic, TOM8 software (Wilke, Holland, Altaye, & Gaser, 2008); and diffeomorphic algorithm (Ashburner, 2007). The resulting template included gray matter and white matter tissue segments registered to the Montreal Neurological Institute MNI152 standard brain space. The gray matter part of the template was also used to create a binary gray matter mask by an 8-mm Gaussian smoothing of the gray matter segment of the template followed by an intensity thresholding with a value of 0.3. Lastly, deformation fields, obtained during spatial normalization of individual structural images to the group template, were applied to the functional images, which were also resliced to at 3mm cubic voxel and smoothed with an 8mm Gaussian kernel.

Participants with excessive head motion, estimated as a mean frame wise displacement exceeding 2 SD of the sample mean, were excluded from the analysis of the concurrent fMRI session data. Therefore, 2 adolescents born very preterm and

2 controls were excluded from the right-hand finger opposition dataset; 3 adolescents born very preterm and 1 control from the left-hand finger opposition dataset; 2 adolescents born very preterm and 3 controls from the right-hand diadochokinesis dataset; and 2 adolescents born very preterm and 1 control from left-hand diadochokinesis dataset. One of the participants born very preterm was scanned only in the right-hand finger opposition session. The very preterm group and controls were not statistically significantly ($p<0.05$, two tailed t-test) different in mean frame wise displacement in any of these samples.

## 4.3 Statistical analysis

Continuous variables were described by means (SD) or medians (minimum, maximum) depending on their distribution. The normality of the distributions was assessed both graphically and with the Shapiro-Wilk test. Categorical variables were described with frequencies (n, %). The Independent Sample T-test or the Mann-Whitney U-test were used to study the difference in continuous variables between compared groups. For the categorical variables chi-square test or Fisher's exact test was used. Correlations between two continuous variables were calculated using Pearson or Spearman's correlation.

Linear regression was used to study the associations between the continuous HINE global score and continuous outcome variables (the Movement ABC-2, full-scale IQ, and four indexes of the WISC-IV). Logistic regression was used to study the association between the continuous HINE global score and categorical outcome variable (typical neurological outcome or complex MND) and between the 11-year outcomes (typical neurological outcome vs complex MND and continuous full-scale IQ). The analyses were adjusted for sex, brain MRI findings at term, paternal education, and birth weight z-score since these have previously been found to be associated with cognition at 11 years in children born very preterm in this cohort (Nyman et al., 2017). In addition, associations between the background characteristics (Table 3) and DCD were studied using logistic regression analysis. The associations between motor outcome (children born very preterm with and without DCD), cognitive outcome (full-scale IQ and indexes as continuous variables) and characteristics (birth weight, gestational age, and mother's and father's education; chosen a priori) were studied using multiple linear regression model. Goodness of fit was reported according to the Akaike information criterion, where information criteria are in a smaller-is-better form. Residuals were checked to justify the analysis. Possible multicollinearity was checked; a correlation coefficient equal to or greater than 0.8 and/or tolerance value less than 0.1 and/or Phi and Cramer's V equal to or greater than 0.8 was considered a sign of multicollinearity. A receiver operating characteristics (ROC) curve and the area under the curve (AUC)

were used as probability curves to evaluate the diagnostic accuracy the HINE for full-scale IQ.

To calculate the 17D total score, multiple imputation was used to replace the missing values with one value (as suggested by the instrument's home page, http://www.15d-instrument.net/15d/replacing-missing-data/), if no more than three dimensions were missing from the 17D. If more than three dimensions were missing, the questionnaire was not used in the analyses. Statistical analyses, excluding the fMRI data analyses, were performed using SAS V.9.4 for Windows and SPSS version 27.0/28.0 (IBM SPSS Statistics, IBM Corporation, NY, USA). A two-tailed p-value of $<0.05$ was considered statistically significant.

The fMRI data for each hand coordination task and hand were analyzed separately. Statistical analyses were performed in SPM12 in two stages. First, a general linear model was built for each individual that included four 19s epochs of a motor task while the control condition was modelled implicitly. To account for the impact of head motion, the model included 6 realignment parameters, their Euclidian norm, and dummy regressors for scans with scan-to-scan changes in global mean $z>4$; translation >2 mm; rotation >1 degree (0.0175 rad) as provided by the Artifact Detection Tools software (https://www.nitrc.org/projects/artifact_detect). The condition regressor was convolved with the hemodynamic response function. A high-pass filter with a cut-off period of 128s was applied to account for a low frequency scanner drift. The model was estimated for each participant and individual contrast images of between-condition activation differences were fed into the second-level group analysis treating subjects as a random factor. All second level models included mean frame wise displacement as a nuisance covariate to account for individual difference in head movement. Activation patterns for each task-hand combination were obtained for the whole brain within each group with One-Sample T-tests and a voxel threshold of $p<0.05$ after family-wise error correction for multiple comparisons. These were visually inspected to ensure the patterns met the general expectation for the tasks used. Further analyses were performed within the ROI. The group differences were explored when controlling for gender using full factorial ANCOVA models to obtain the main effects and interactions. A linear relationship between the fMRI signal and gestational age in each task-hand combination was analyzed within the very preterm group with and without adjusting for gender. A permutation-based non-parametric Threshold-Free Cluster Enhancement method (Smith & Nichols, 2009), as implemented in the Threshold-Free Cluster Enhancement method Toolbox (Christian Gaser, Jena University Hospital, Germany), was applied to calculate a combined voxel-cluster statistic using 5000 permutations and family-wise error corrected significance threshold of $p<0.05$. To check and illustrate a direction and size of significant effects in the analyses, we calculated mean cluster values and 90% confidence intervals for significant clusters

obtained in the Independent Sample T-test and ANCOVA analyses, as well as slope values and residuals obtained in regression analyses with the Marsbar software (Brett et al., 2002).

## 4.4 Ethics

The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000, 2012 and 2016. Written informed consents for the studies included in this thesis were provided by the parents and children.

# 5 Results

## 5.1 Characteristics of the participants

In Studies I and II, only children born very preterm were included. The characteristics of the children participating in Studies I and II are shown in Table 3.

**Table 3.** Characteristics of children born very preterm (gestational age <32 weeks or birth weight ≤1500 grams) participating in Studies I and II. (Modified from Studies I and II.)

| Characteristic | Study cohort, Study I (n=170) | Study cohort, Study II (n=174) |
|---|---|---|
| Gestational age mean (SD), [minimum, maximum], weeks | 29.1 (2.7) [23.0, 35.9] | 29.0 (2.7) [23.0, 35.9] |
| Birth weight mean (SD), [minimum, maximum], grams | 1134.4 (315.3) [400.0, 2120.0] | 1119.2 (314.4) [400.0, 2120.0] |
| Small for gestational age (≤2SD), n (%) | 56 (32.9) | 58 (33.3) |
| Birth weight z-score, mean (SD), [minimum, maximum] | -1.4 (1.5) [-4.9, 3.4] | -1.4 (1.5) [-4.9, 3.4] |
| Male, n (%) | 94 (55.3) | 95 (54.6) |
| Caesarean delivery, n (%) | 101 (59.4) | 106 (60.9) |
| Bronchopulmonary dysplasia, n (%) | 22 (12.9) | 24 (13.8) |
| Operated necrotizing enterocolitis, n (%) | 7 (4.2) | 7 out of 171 (4.1) |
| Sepsis, n (%) | 30 (17.7) | 31 (17.8) |
| Laser-treated retinopathy of prematurity, n (%) | 4 (2.4) | 5 out of 163 (3.1) |
| Major brain pathologies on MRI at term, n (%)* | 42 out of 165 (25.5) | 45 out of 169 (26.6) |
| Mother's education >12 years, n (%) | 107 out of 168 (63.7) | 109 out of 172 (63.4) |
| Father's education >12 years, n (%) | 56 out of 166 (33.7) | 56 out of 170 (32.9) |
| Cerebral palsy, diagnosed by 2 years of corrected age, n (%) | 9 (5.3) | 9 (5.2) |

MRI – magnetic resonance imaging

*The classification of the MRI findings at term are presented in Table 1.

The characteristics shown in Table 3 were compared between the study children and the children who withdrew. In Study I, the mothers of the study children had a higher educational level compared with the mothers of the children who withdrew

(63.7% vs 46.7% with >12 years of education, p=0.04). In Study II, the study children had a lower birth weight compared with the children who withdrew (birth weight mean 1119.2 grams vs 1226.3 grams, p=0.05) and the mothers of the study children had a higher educational level (63.4% vs 46.5% with >12 years of education, p=0.04). In Study I, the follow-up rate was 77.6% (170 out of 219 eligible participants) and in Study II the follow-up rate was 78.7% (174 out of 221 eligible participants).

In Study III, both the adolescents born very preterm and controls born at term were included. The characteristics of the adolescents born very preterm and the controls are shown in Table 4.

**Table 4.** Characteristics of adolescents born very preterm (gestational age <32 weeks or birth weight ≤1500 grams) and controls born at term participating Study III. (Modified from Study III.)

| Characteristic | Adolescents born very preterm (n=34) | Control adolescents born at term |
|---|---|---|
| Gestational age mean (SD), [minimum, maximum], weeks | 29.2 (2.8) [24.7, 34.0] | 40.1 (1.2) [37.1, 42.1] |
| Birth weight mean (SD), [minimum, maximum], grams | 1180.6 (347.9) [620.0, 2120.0] | 3611.6 (456.4) [2830.0, 4580.0] |
| Male, n (%) | 20 (58.8) | 20 (54.1) |

In Study III, the characteristics including gestational age, birth weight, sex, small for gestational age status, multiple birth, cesarean delivery, bronchopulmonary dysplasia, operated necrotizing enterocolitis, sepsis, laser-treated retinopathy of prematurity, brain MRI findings at term, and mother's and father's educational level were compared with the adolescents born very preterm participating in the study and the adolescents born very preterm who withdrew. No statistically significant differences in these characteristics were found.

## 5.2 Neurological outcome at 2 years of corrected age

At 2 years of corrected age, 174 children born very preterm were examined with the HINE. The HINE global score and subsection scores at 2 years of corrected age are shown in Figure 3. The median HINE global score of all 174 study children was 74.1 (minimum 38.0, maximum 78.0). Of these children, nine (5.2%) were diagnosed with CP by 2 years of age. In these children with CP, the median HINE global score was 56.0 (minimum 38.0, maximum 74.0). The severity of CP was based on the GMFCS. Four children were classified as level I, three as level II, and two as level IV.

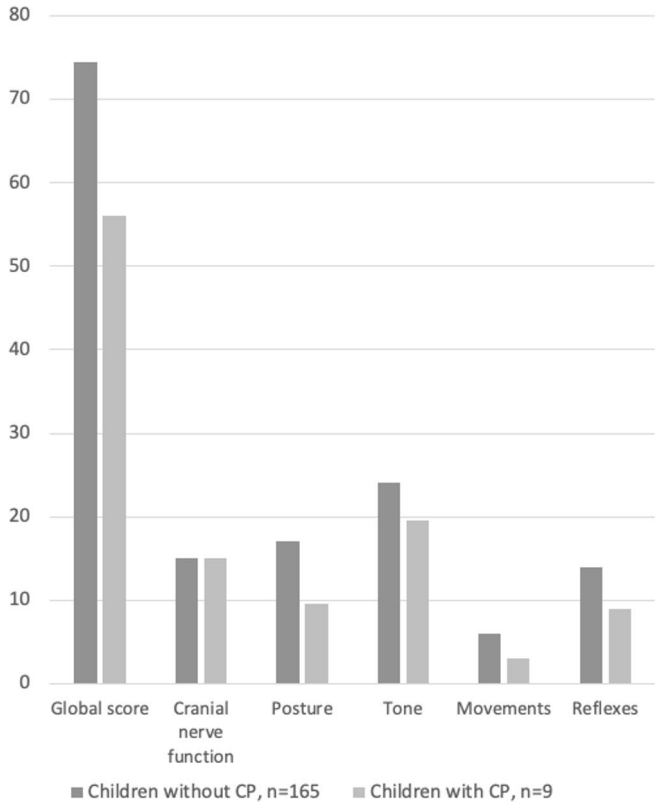



**Figure 3.** The median HINE scores at 2 years of corrected age in children born very preterm without and with CP.

## 5.3 Neurodevelopment at 11 years

### 5.3.1 Motor outcome

The motor outcomes of 11-year-old children born very preterm without CP are shown in Table 5. The children with the Movement ABC-2 total test score >5th percentile were classified as having a typical motor outcome. However, since a total test score >5th to 15th percentile indicates a risk of movement difficulties, the group size of the children with test scores >5th to 15th percentile was also calculated. A test score ≤5th percentile denoted DCD. All the children, including those with full-scale IQ<70, were able to follow the instructions of the Movement ABC-2. Therefore, children with full-scale IQ <70 were included in the analysis regarding motor outcome, as this is also recommended by the European Academy of Childhood Disability (Blank et al., 2019).

Eight of the nine children with a diagnosed CP were successfully assessed with the Movement ABC-2; however, the children with CP (n=9) were analyzed as their

own group and not as a part of the group of children with DCD. In addition, one of the children without CP did not complete the Movement ABC-2 due to a recent surgical operation.

Of the characteristics shown in Table 3, DCD was associated with male sex ($p<0.01$), lower gestational age ($p=0.04$), bronchopulmonary dysplasia ($p=0.04$) sepsis ($p=0.04$) and major brain pathologies on an MRI at term ($p=0.02$). Of the 18 children with DCD, 8 had major brain pathology on MRI at term.

**Table 5.** Motor outcomes of 11-year-old children born very preterm (n=160) at 11 years of age according to the Movement Assessment Battery for Children 2. Children with cerebral palsy are not included.

| Motor outcome | Number of children, n (%) |
|---|---|
| Typical motor outcome i.e. >5th percentile<br>*Risk of movement difficulties, >5th to 15th percentile* | 142 (88.8)<br>*12/142 (8.5)* |
| DCD i.e. ≤5th percentile | 18 (11.3) |

DCD – developmental coordination disorder

The HINE global score and subsection scores at 2 years of corrected age were compared according to the motor outcome assessed with the Movement ABC-2 at 11 years of age. When all the study children were included in the analysis, the HINE global score at 2 years correlated positively with the percentiles of the Movement ABC-2 at 11 years ($r=0.24$, $p=0.002$). When children with CP were excluded, this correlation did not remain statistically significant ($r=0.12$, $p=0.1$). The HINE scores according to the subsequent motor outcome are shown in Table 6. When children with CP were excluded, no difference in the HINE global score and subsection scores were found between the children with and without DCD.

**Table 6.** The HINE scores at 2 years of corrected age according to the motor outcome assessed with the Movement ABC-2 at 11 years in children born very preterm. Children with cerebral palsy are not included. (From Original publication II.)

| The HINE median (minimum, maximum) | Typical motor outcome (n=140) | DCD (n=18) | p-value |
|---|---|---|---|
| Global score | 74.5 (67.5, 78.0) | 74.3 (66.0, 76.5) | 0.5 |
| Cranial nerve function | 15.0 (12.0, 15.0) | 15.0 (13.0, 15.0) | 0.3 |
| Posture | 17.0 (14.0, 18.0) | 16.5 (13.5, 18.0) | 0.06 |
| Tone | 24.0 (18.0, 24.0) | 24.0 (20.0, 24.0) | 0.7 |
| Movements | 6.0 (3.0, 6.0) | 6.0 (5.0, 6.0) | 0.2 |
| Reflexes | 14.0 (9.0, 15.0) | 14.0 (11.0, 15.0) | 0.7 |

DCD – developmental coordination disorder
HINE – The Hammersmith Infant Neurological Examination
Movement ABC-2 – The Movement Assessment Battery for Children – Second Edition

### 5.3.2 Neurological outcome

The neurological outcomes of 11-year-old children born very preterm, evaluated with the Touwen neurological examination, are shown in Table 7. The typical neurological outcome included children with a neurologically typical result and children with simple MND. Similarly to the motor assessment, eight of the nine children with CP were successfully assessed with the Touwen neurological examination but analyzed as a separate group from those with complex MND. Further, the diagnosis of CP was re-evaluated at 11 years and confirmed in all cases without any changes.

**Table 7.** Neurological outcomes of 11-year-old children born very preterm (n=167) according to the Touwen neurological examination or previously diagnosed cerebral palsy (CP).

| Neurological outcome | Number of children, n (%) |
|---|---|
| Typical neurological outcome | 127 (76.5) |
| *neurologically typical* | *63/127 (49.6)* |
| *Simple MND* | *64/127 (50.4)* |
| Complex MND | 31 (18.7) |
| CP | 9 (5.4) |

CP – cerebral palsy
MND – minor neurological dysfunction

The HINE global score and subsection scores at 2 years were compared with the neurological outcome assessed with the Touwen neurological examination at 11 years of age. When all the study children were included, higher HINE global score at 2 years was associated with a decreased risk for complex MND at 11 years (OR=0.9, 95%CI 0.8–0.9, p=0.001), also when adjusted for gender, brain MRI findings at term, paternal education, and birth weight z-score (OR=0.8, 95%CI 0.7–0.9, p=0.001). When the children with CP were excluded, the association between the HINE global score and subsequent neurological outcome did not remain statistically significant.

The HINE scores according to the neurological outcome at 11 years are shown in Table 8. When the children with CP were excluded, the HINE posture subsection score at 2 years was higher in children with a typical neurological outcome at 11 years compared to 11-year-olds with complex MND (median 17.0 vs 16.5, p=0.002).

**Table 8.** The HINE scores at 2 years of corrected age according to the neurological outcome assessed with the Touwen neurological examination at 11 years in children born very preterm. Children with cerebral palsy are not included. (From original publication II.)

| The HINE median (minimum, maximum) | Typical neurological outcome (n=127) | Complex MND (n=31) | p-value |
|---|---|---|---|
| Global score | 74.5 (67.5, 78.0) | 74.0 (66.0, 78.0) | 0.3 |
| Cranial nerve function | 15.0 (12.0, 15.0) | 15.0 (12.5, 15.0) | 0.8 |
| Posture | 17.0 (13.5, 18.0) | 16.5 (14.0, 18.0) | 0.002 |
| Tone | 24.0 (18.0, 24.0) | 24.0 (20.0, 24.0) | 0.3 |
| Movements | 6.0 (3.0, 6.0) | 6.0 (5.0, 6.0) | 0.6 |
| Reflexes | 14.0 (9.0, 15.0) | 14.0 (11.0, 15.0) | 0.3 |

HINE – The Hammersmith Infant Neurological Examination
MND – minor neurological dysfunction

### 5.3.3 Cognitive outcome

The cognitive outcome of 11-year old children assessed with the WISC-IV is shown in Table 9. Of the nine children with CP, five (55.6%) had a full-scale IQ <70. The distribution of the full-scale IQ in children without CP is shown in Table 10.

**Table 9.** Cognitive outcome of 11-year-old children born very preterm. The cognitive outcome is assessed with the Wechsler Intelligence Scale for Children – Fourth Edition.

| The WISC-IV | Children without cerebral palsy (n=165) | Children with cerebral palsy (n=9) |
|---|---|---|
| Full-scale IQ mean (SD), [minimum, maximum] | 89.1 (16.2) [40.0, 131.0] | 62.4 (22.8) [40.0, 97.0] |
| Verbal comprehension mean (SD), [minimum, maximum] | 90.6 (14.1) [46.0, 122.0] | 75.1 (21.1) [46.0, 98.0] |
| Perceptual reasoning mean (SD), [minimum, maximum] | 93.1 (15.8) [51.0, 122.0] | 64.8 (23.1) [40.0, 100.0] |
| Working memory mean (SD), [minimum, maximum] | 93.1 (16.1) [46.0, 133.0] | 77.0 (20.5) [46.0, 109.0] |
| Processing speed mean (SD), [minimum, maximum] | 94.7 (16.7) [47.0, 153.0] | 72.4 (21.4) [47.0, 106.0] |

IQ – intelligence quotient

**Table 10.** Distribution of the full-scale IQs in children born very preterm without cerebral palsy.

| Full-scale IQ | Number of children, n (%) (n=161) |
|---|---|
| Average range, full-scale IQ ≥90 | 89 (55.3) |
| Low average, full-scale IQ ≥80–89 | 34 (21.1) |
| Borderline, full-scale IQ ≥70–79 | 25 (15.5) |
| Severe cognitive impairment, full-scale IQ <70 | 13 (8.1) |

IQ – intelligence quotient

The HINE global score and subsection scores at 2 years were compared with the cognitive outcome assessed with the WISC-IV at 11 years, as shown in Table 11. The children with normal cognitive outcome had a higher HINE global score (median 74.5 vs 73.0, p=0.02) and a higher posture subsection score (median 17.0 vs 16.0, p=0.007) compared to the children with severe cognitive impairment i.e. full-scale IQ <70.

**Table 11.** The HINE scores at 2 years of corrected age according to the cognitive outcome assessed with the WISC-IV at 11 years in children born very preterm. Children with cerebral palsy are not included. (From original publication II.)

| The HINE median (minimum, maximum) | Normal cognitive outcome (n=150) | Severe cognitive impairment (n=15) | p-value |
|---|---|---|---|
| Global score | 74.5 (67.5, 78.0) | 73.0 (66.0, 75.5) | 0.02 |
| Cranial nerve function | 15.0 (12.0, 15.0) | 15.0 (13.0, 15.0) | 0.9 |
| Posture | 17.0 (13.5, 18.0) | 16.0 (14.0, 18.0) | 0.007 |
| Tone | 24.0 (18.0, 24.0) | 23.0 (19.0, 24.0) | 0.1 |
| Movements | 6.0 (3.0, 6.0) | 6.0 (5.0, 6.0) | 0.1 |
| Reflexes | 14.0 (9.0, 15.0) | 14.0 (11.0, 15.0) | 0.3 |

HINE – The Hammersmith Infant Neurological Examination
WISC-IV – The Wechsler Intelligence Scale for Children – Fourth Edition

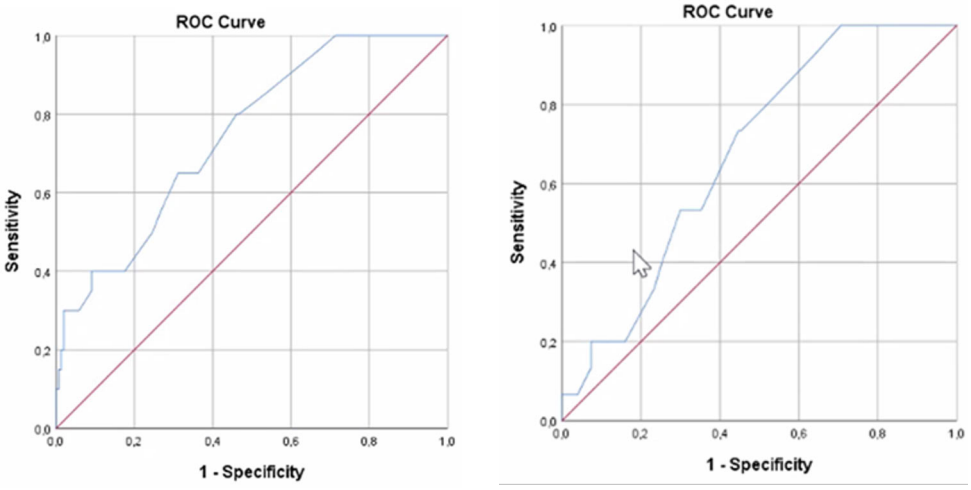
The HINE global score at 2 years and its association with the mean values of the full-scale IQ and its four indexes assessed with the WISC-IV at 11 years is shown in Table 12. A higher HINE global score at 2 years was associated with better full-scale IQ, verbal comprehension, and perceptual reasoning at 11 years even when the children with CP were excluded. When the HINE global score was increased by one point the full-scale IQ was improved by 1.2 points (b=1.2, 95% confidence interval 0.3–2.1, p=0.01).

**Table 12.** The HINE global score at 2 years of corrected age in association with the mean values of full-scale IQ and its four indexes assessed with the WISC-IV at 11 years in children born very preterm. (Modified from Study II.)

| The WISC-IV | All study children (n=174) | The HINE global score at 2 years | Children without CP (n=165) | The HINE global score at 2 years |
|---|---|---|---|---|
| | *Mean (SD) [minimum, maximum]* | *b=regression coefficient* | *Mean (SD) [minimum, maximum]* | *b=regression coefficient* |
| Full-scale IQ | 87.7 (17.6) [40.0, 131.0 | b=1.2, 95% CI 0.8–1.7, p<0.001 | 89.1 (16.2) [40.0, 131.0 | b=1.2, 95% CI 0.3–2.1, p=0.01 |
| Verbal comprehension | 89.8 (14.9) [46.0, 122.0] | b=0.7, 95% CI 0.4–1.1, p<0.001 | 90.6 (14.1) [46.0, 122.0] | b=1.0, 95% CI 0.2–1.8, p=0.02 |
| Perceptual reasoning | 91.6 (17.3) [40.0, 122.0] | b=1.3, 95% CI 0.8–1.7, p<0.001 | 93.1 (15.8) [51.0, 122.0] | b=1.3, 95% CI 0.4–2.2, p=0.006 |
| Working memory | 92.2 (16.7) [46.0, 133.0] | b=0.6, 95% CI 0.2–1.1, p=0.008 | 93.1 (16.1) [46.0, 133.0] | b=0.5, 95% CI -0.5–1.4, p=0.3 |
| Processing speed | 93.6 (17.6) [47.0, 153.0] | b=1.1, 95% CI 0.6–1.5, p<0.001 | 94.7 (16.7) [47.0, 153.0 | b=0.7, 95% CI -0.3–1.7, p=0.2 |

CI – confidence interval
CP – cerebral palsy
HINE – The Hammersmith Infant Neurological Examination
IQ – intelligence quotient
WISC-IV – The Wechsler Intelligence Scale for Children – Fourth Edition

The ROC curves showing the ability of the HINE at 2 years in detecting severe cognitive impairment (full-scale IQ<70) at 11 years is shown in Figure 4. The ROC curve on the right side represents the data of all the children; the area under the ROC curve (AUC) was 0.75 (95% CI 0.64–0.85, p<0.001). The ROC curve on the left side represents the data of children without CP; the AUC was 0.68 (95% CI 0.56–0.79, p=0.02).




All children Children without CP

**Figure 4.** The ROC curves showing the ability of the HINE at 2 years in detecting severe cognitive impairment (full-scale IQ <70) in children born very preterm at 11 years. The ROC curve on the left side includes the data of children with cerebral palsy (CP); the ROC curve on the right side includes the data of children without CP.

The cognitive outcome of the 11-year-old children without CP according to the concurrent motor outcome is shown in Table 13. The children with DCD had lower scores in the full-scale IQ (p<0.001) as well as in all four indexes including verbal comprehension (p=0.02), perceptual reasoning (p=0.02), working memory (p<0.001), and processing speed (p=0.001). The results remained the same after adjusting for gestational age, birth weight, and mother's and father's education. Severe cognitive impairment was more common in children with DCD compared to the children with typical motor outcome (38.9% vs 3.5%, p<0.001).

**Table 13.** Cognitive outcome assessed with the WISC-IV at 11 years according to the concurrent motor outcome assessed with the Movement ABC-2. Children with cerebral palsy were excluded. (Modified from Study I).

| The WISC-IV | Typical motor outcome (n=142) | DCD (n=18) | p-value |
|---|---|---|---|
| Full-scale IQ mean (SD), [minimum, maximum] | 91.6 (14.3) [52.0, 131.0] | 76.8 (18.2) [40.0, 100.0] | <0.001 |
| Verbal comprehension mean (SD), [minimum, maximum] | 92.1 (13.4) [60.0, 122.0] | 83.8 (16.3) [46.0, 108.0] | 0.02 |
| Perceptual reasoning mean (SD), [minimum, maximum] | 94.8 (14.6) [62.0, 122.0] | 85.7 (17.9) [51.0, 109.0] | 0.02 |
| Working memory mean (SD), [minimum, maximum] | 95.4 (15.0) [55.0, 133.] | 79.2 (13.9) [46.0, 97.0] | <0.001 |
| Processing speed mean (SD), [minimum, maximum] | 96.5 (15.5) [56.0, 153.0] | 83.3 (19.4) [47.0, 118.0] | 0.001 |
| Full-scale IQ <70, n (%) | 5 (3.5) | 7 (38.9) | <0.001 |

DCD – developmental coordination disorder
IQ – intelligence quotient
Movement ABC-2 – The Movement Assessment Battery for Children – Second Edition
WISC-IV – The Wechsler Intelligence Scale for Children – Fourth Edition

The cognitive outcome according to the concurrent neurological outcome of the 11-year-old children without CP is shown in Table 14. The cognitive outcomes of the children with a typical neurological outcome were compared with the cognitive outcomes of the children with complex MND. The children with a typical neurological outcome had higher scores in the full-scale IQ (p=0.001), perceptual reasoning (p=0.002), and working memory (p<0.001) compared to the children with complex MND, as shown in Table 14. The severe cognitive impairment was more common in children with complex MND compared to the children with typical neurological outcome (25.8% vs 3.1%, p<0.001).

**Table 14.** Cognitive outcome of the children born very preterm at 11 years of age according to the concurrent neurological outcome. Cognitive outcome is assessed with the WISC-IV and neurological outcome with the Touwen neurological examination. Children with cerebral palsy were excluded.

| The WISC-IV | Typical neurological outcome (n=127) | Complex MND (n=31) | p-value |
|---|---|---|---|
| Full-scale IQ mean (SD), [minimum, maximum] | 91.9 (14.1), [51.0, 131.0] | 81.3 (18.2), [40.0, 119.0] | 0.001 |
| Verbal comprehension mean (SD), [minimum, maximum] | 91.7 (13.2), [60.0, 122.0] | 88.5 (17.1), [46.0, 120.0] | 0.3 |
| Perceptual reasoning mean (SD), [minimum, maximum] | 95.6 (14.8), [55.0, 122.0] | 86.1 (14.9), [51.0, 109.0] | 0.002 |
| Working memory mean (SD), [minimum, maximum] | 96.2 (14.6), [55.0, 133.0] | 82.1 (15.3), [46.0, 118.0] | <0.001 |
| Processing speed mean (SD), [minimum, maximum] | 96.3 (15.8), [56.0, 153.0] | 90.0 (18.8), [47.0, 118.0] | 0.6 |
| Full-scale IQ <70, n (%) | 4 (3.1) | 8 (25.8) | <0.001 |

IQ – intelligence quotient
MND – minor neurological dysfunction
WISC-IV – The Wechsler Intelligence Scale for Children – Fourth Edition

## 5.4 Self-experienced health-related quality of life at 11 years

The 17D questionnaire was completed at 11 years of age by 167 children born very preterm. Compared to the Finnish normative population (Apajasalo et al., 1996), the study children born very preterm had better self-experienced HRQoL. The children born very preterm reported better results in overall 17D score and the domains of sleeping, discomfort and symptoms, depression, vitality, appearance, and friends and concentration, whereas the normative 11-year-old population reported better results in the domains of eating and distress (Figure 5).

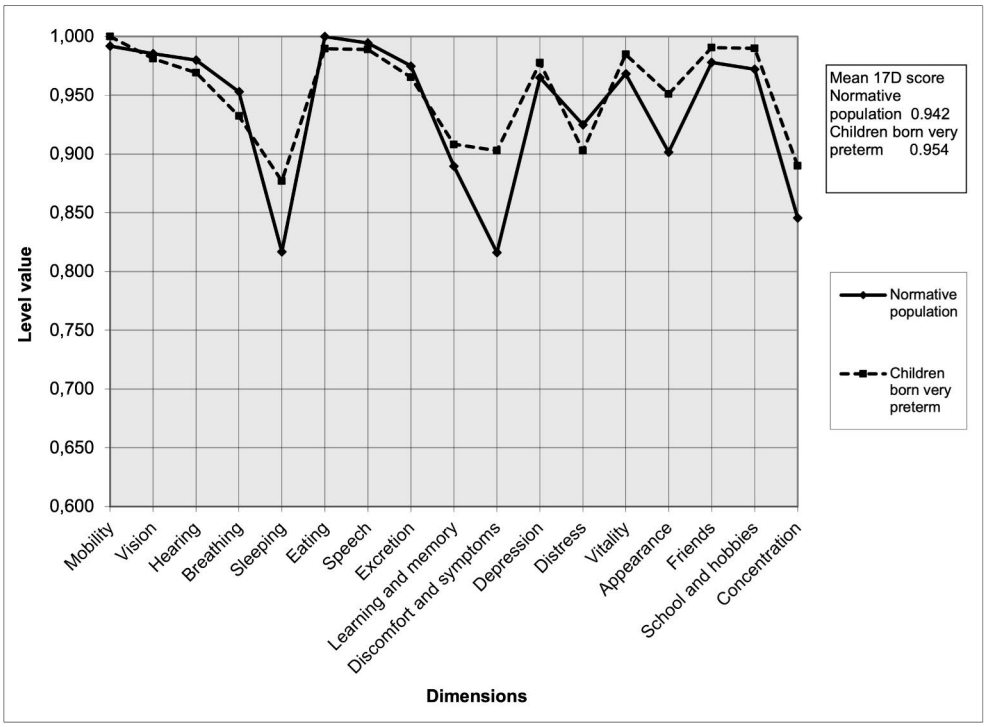



**Figure 5.** The self-experienced HRQoL in 11-year-old study children born very preterm and in the Finnish normative population of 11-year-old children (courtesy of Harri Sintonen).

When all the study children were included, a positive correlation between the Movement ABC-2 and the 17D questionnaire was obtained (r=0.2, p=0.04). The correlation between the Movement ABC-2 and the 17D questionnaire did not remain statistically significant when the children born very preterm with CP were excluded (r=0.1, p=0.06). No correlation between the full-scale IQ and the 17D questionnaire was found (r=0.07, 0.4).

The children with a typical motor outcome had a higher overall score of the 17D questionnaire compared to children with DCD (0.96 vs 0.93, p=0.04). The overall scores of the 17D questionnaire were not statistically significantly different between the children with a typical motor outcome and children with CP (0.96 vs 0.94, p=0.5) nor between the children with DCD and children with CP (0.93 vs 0.94, p=0.6).

When all the study children were included, the overall score of the 17D questionnaire was 0.96 in children born very preterm with a normal cognitive outcome and 0.93 in children with full-scale IQ<70; no statistically significant difference was found in these overall scores of the 17D questionnaire (p=0.1). When the children born very preterm with CP were excluded, the overall scores of 17D questionnaire remained at 0.96 in children born very preterm with a normal cognitive outcome and 0.93 in children with full-scale IQ<70, showing no statistically significant difference (p=0.2).

## 5.5 Hand coordination skills at 13 years

The hand coordination skills were assessed of 34 adolescents born very preterm and also of 37 control adolescents born full-term at 13 years of age. The characteristics of adolescents born very preterm and the controls are shown in Table 4. The results of the hand coordination skills are presented in Table 15. The results show a high rate of associated movements in both adolescents born very preterm and controls. No statistically significant differences in the hand coordination skills between the adolescents born very preterm and the controls were found.

**Table 15.** The rates of abnormal hand coordination skills at 13 years of adolescents born very preterm (n=34) and controls born full-term (n=37).

| Hand coordination task | Abnormal performance, adolescents born very preterm (n=34) | Abnormal performance, controls (n=37) | p-value |
|---|---|---|---|
| **Finger opposition, right hand** | | | |
| *Smoothness, n (%)* | 0 (0) | 0 (0) | 1.0 |
| *Transition, n (%)* | 1 (2.9) | 0 (0) | 0.5 |
| *Associated movements, n (%)* | 11 (32.4) | 12 (32.4) | 1.0 |
| **Finger opposition, left hand** | | | |
| *Smoothness, n (%)* | 0 (0) | 0 (0) | 1.0 |
| *Transition, n (%)* | 1 (2.9) | 0 (0) | 0.5 |
| *Associated movements, n (%)** | 9 out of 33 (27.3) | 18 (48.6) | 0.07 |
| **Diadochokinesis, right hand*** | | | |
| *Performance, n (%)* | 2 out of 33 (6.1) | 0 (0) | 0.2 |
| *Associated movements, n (%)* | 9 out of 33 (27.3) | 17 (45.9) | 0.1 |
| **Diadochokinesis, left hand*** | | | |
| *Performance, n (%)* | 2 out of 33 (6.1) | 1 (2.7) | 0.6 |
| *Associated movements, n (%)* | 14 out of 33 (42.4) | 22 (59.5) | 0.6 |

*Data missing for one adolescent

## 5.6 Functional magnetic resonance imaging at 13 years

The fMRI data during hand coordination tasks at 13 years was available for 30/32 (adolescents born very preterm/controls) regarding finger opposition of the right-hand, 29/31 finger opposition of the left-hand, 28/32 diadochokinesis of the right-hand, and 29/33 diadochokinesis of the left-hand. Only right-handed adolescents were included.

The analysis showed that, in the entire grey matter volume within each task-hand-combination, there was a similarity in the location of the activated areas for the same hand tasks. The areas that were activated the most during finger opposition and diadochokinesis in both the adolescents born very preterm and the controls were in the contralateral primary sensorimotor cortex, the bilateral medial and lateral premotor areas, the occipital cortex, and in a part of the cerebellum. The areas most activated are shown in Figure 6 and Figure 7.

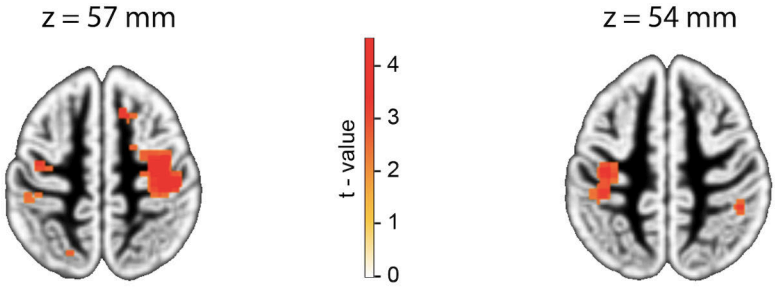



**Figure 6.** Activated areas during finger opposition. Left image shows the areas activated during left hand task; right image shows the areas activated during right hand task. The activated areas are shown according to neurological convention (right is right). The uncorrected voxel threshold p<0.01 was used for illustrative purposes. z – z coordinates of the slices in the Montreal Neurological Institute brain space. (Modified from Study III.)

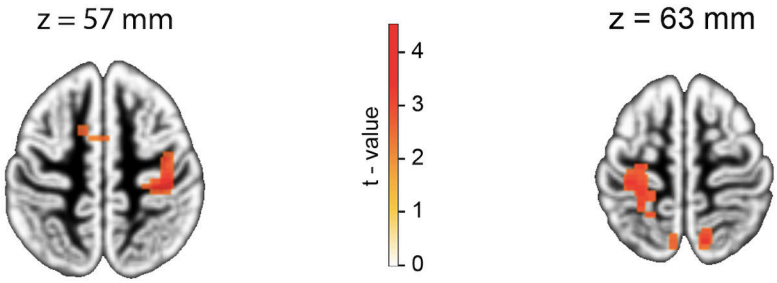



**Figure 7.** Activated areas during diadochokinesis. Left image shows the areas activated during left hand task; right image shows the areas activated during right hand task. The activated areas are shown according to neurological convention (right is right). The uncorrected voxel threshold p<0.01 was used for illustrative purposes. z – z coordinates of the slices in the Montreal Neurological Institute brain space. (Modified from Study III.)

Between-group comparisons of the adolescents born very preterm and controls are shown in Table 16.

**Table 16.** Activation differences in fMRI during hand coordination tasks between the adolescents born very preterm and the controls. In the observed activation differences, the adolescents born very preterm showed stronger activation. (Modified from Study III.)

| Task, (n preterm/ n controls) | Brain area | Cluster size, voxels | TFCE value | p-value, FWE-corrected | MNI x/y/z |
|---|---|---|---|---|---|
| Finger opposition, right hand (30/32) | No significant clusters | | | | |
| Finger opposition, left hand (29/31) | Right precentral gyrus<br>Right precentral gyrus<br>Right postcentral gyrus | 101 | 268.9<br>182.7<br>243.8 | 0.01*<br>0.04<br>0.02* | 30/-18/57<br>27/-9/51<br>39/-27/57 |
| Diadochokinesis, right hand (28/32) | No significant clusters | | | | |
| Diadochokinesis, left hand (29/33) | Right postcentral gyrus | 23 | 193.3 | 0.03* | 33/-30/57 |

fMRI – functional magnetic resonance imaging
TFCE – Threshold-Free Cluster Enhancement statistic
FWE – family-wise error
MNI – Montreal Neurological Institute
*Statistically significant also when adjusted with gender

During hand coordination tasks of the dominant i.e. right hand, no differences in brain activation were found between the adolescents born very preterm and controls. During the non-dominant i.e. left-hand tasks, the group of adolescents born very preterm showed stronger activation in the right precentral gyrus ($p=0.01$) and in the right postcentral gyrus ($p=0.02$) during finger opposition (Figure 8) and stronger activation in the right postcentral gyrus ($p=0.03$) during diadochokinesis compared with the controls (Figure 9). These results remained statistically significant even when adjusted for gender.

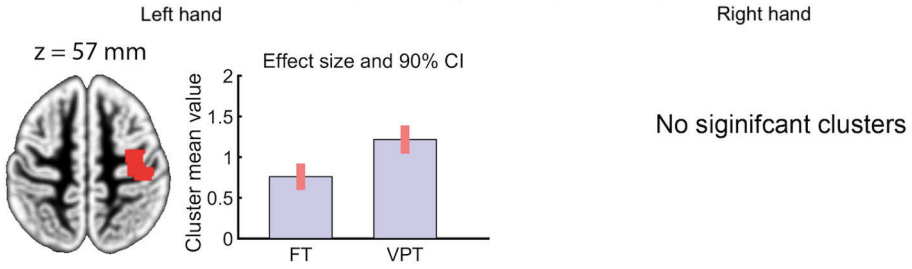



**Figure 8.** Comparisons of the brain activation during finger opposition between the adolescents born very preterm and controls born full-term. The activated area is shown according to neurological convention (right is right). z – z coordinates of the slices in the Montreal Neurological Institute brain space; FT – control adolescents born full-term; VPT – adolescents born very preterm. (Modified from Study III.)

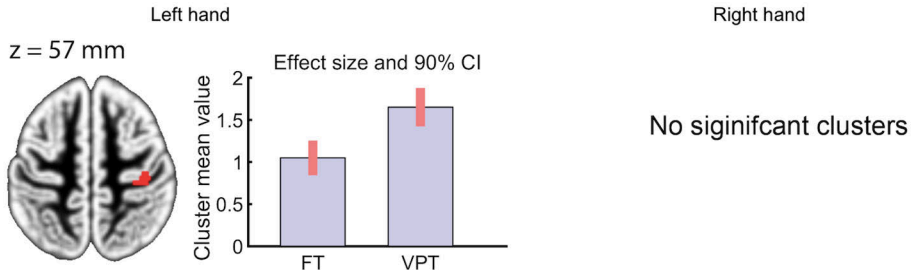



**Figure 9.** Comparisons of the brain activation during diadochokinesis between the adolescents born very preterm and controls born full-term. The activated area is shown according to neurological convention (right is right). z – z coordinates of the slices in the Montreal Neurological Institute brain space; FT – control adolescents born full-term; VPT – adolescents born very preterm. (Modified from Study III.)

The activation differences within the adolescents born very preterm are shown in Table 17. In adolescents born very preterm, no association was found between the gestational age and the brain activation during finger opposition of the right hand. Lower gestational age was associated with reduced activation in the left superior parietal lobule (p=0.02), regarding diadochokinesis of the right hand (Figure 10). The result remained the same when adjusted for gender. Regarding the left hand tasks of the adolescents born very preterm, a lower gestational age was associated with stronger activation in the right cerebellar lobule V (p=0.03) and the left cerebellar lobule VI (p=0.03) during finger opposition (Figure 11), and with stronger activation in the right superior parietal lobule (p=0.03) during diadochokinesis (Figure 12).

**Table 17.** Activation differences in fMRI during hand coordination tasks in adolescents born very preterm. (Modified from Study III.)

| Task, n | Brain areas (Activation-gestational age relationship) | Cluster size, voxels | TFCE value | p-value, FWE-corrected | MNI x/y/z |
|---|---|---|---|---|---|
| Finger opposition, right hand, 30 | No significant clusters | | | | |
| Finger opposition, left hand, 29 | Right cerebellar lobule V<br>Right cerebellar lobule V<br>Left cerebellar lobule VI (Negative) | 67 | 265.1<br>228.2<br>263.0 | 0.03*<br>0.04*<br>0.03* | 6/-63/-15<br>12/-72/-15<br>-9/-66/-21 |
| Diadochokinesis, right hand, 28 | Left superior parietal lobule<br>Left superior parietal lobule<br>Left superior parietal lobule (Positive) | 28 | 273.3<br>234.2<br>225.7 | 0.02*<br>0.03<br>0.04 | -9/-69/57<br>-24/-66/51<br>-15/-63/51 |
| Diadochokinesis, left hand, 29 | Right superior parietal lobule<br>Right superior parietal lobule (Negative) | 31 | 239.7<br>227.9 | 0.03<br>0.04 | 17/-54/66<br>30/-48/63 |

fMRI – functional magnetic resonance imaging
TFCE – Threshold-Free Cluster Enhancement statistic
FWE – family-wise error
MNI – Montreal Neurological Institute
*Statistically significant also when adjusted with gender

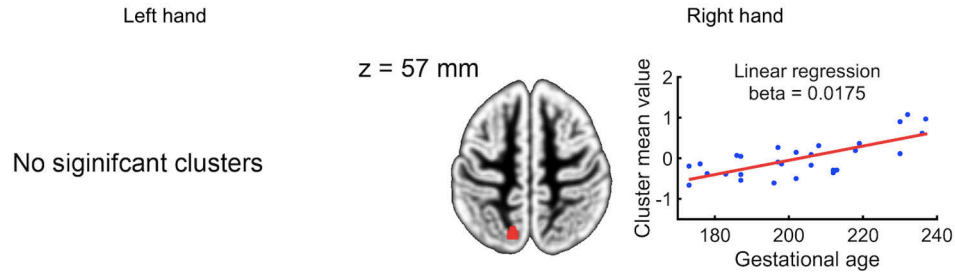



**Figure 10.** The association between the brain activation and gestational age during diadochokinesis in adolescents born very preterm. Lower gestational age was associated with reduced activation in the left superior parietal lobule during right hand diadochokinesis. The activated area is shown according to neurological convention (right is right). (Modified from Study III.)

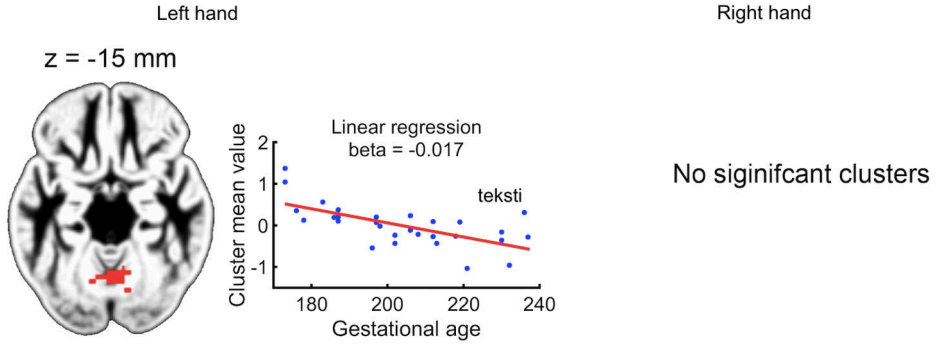



**Figure 11.** The association between the brain activation and gestational age during finger opposition in adolescents born very preterm. Lower gestational age was associated with stronger activation in the right cerebellar lobule V and the left cerebellar lobule VI during left hand finger opposition. The activated areas are shown according to neurological convention (right is right). (Modified from Study III.)

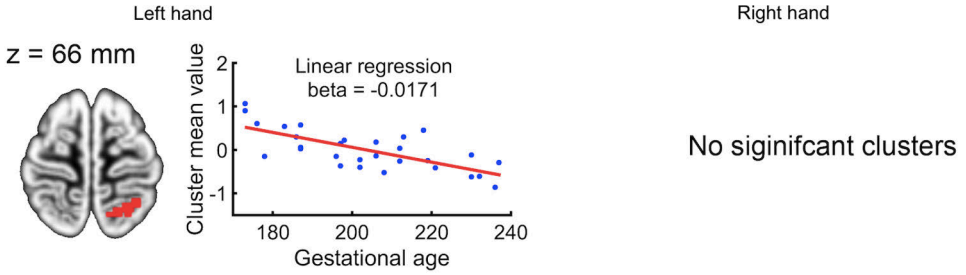



**Figure 12.** The association between the brain activation and gestational age during diadochokinesis in adolescents born very preterm. Lower gestational age was associated with stronger activation in the right superior parietal lobule during left hand diadochokinesis. The activated area is shown according to neurological convention (right is right). (Modified from Study III.)

# 6 Discussion

This thesis showed that, in this regional cohort of children born very preterm in Turku University Hospital from 2001 to 2006, the majority of the children had typical neurodevelopment i.e. neurological, motor and cognitive outcome at 11 years of age. However, it was shown that 11-year-old children born very preterm in 2000s had an increased risk for neurodevelopmental impairments compared to the general population. This thesis also showed that a better neurological outcome at 2 years of corrected age was associated with better general intelligence at 11 years in children born very preterm. Further, at 11 years of age, severe cognitive impairment was more common in children with concurrent DCD or complex MND compared to peers born very preterm without these impairments.

The hand coordination skills, including finger opposition and diadochokinesis evaluated according to the Touwen neurological examination, of adolescents born very preterm did not differ from controls born full-term at 13 years of age. The fMRI showed that participants born very preterm had stronger activation in the contralateral primary sensorimotor cortex during left-hand coordination tasks than controls born at term. Moreover, within the adolescents born very preterm, the cerebellar and superior parietal activations were associated with gestational age.

## 6.1 Neurological outcome at 2 years of corrected age

In this cohort of children born very preterm, the rate of CP was 5%. The diagnosis of CP was confirmed without any changes at 11 years of age in all cases. The rate of CP in this study is similar with a recent study by Twilhaar et al. (2022), which reported that the rate of CP was 5% in a French cohort of 5-year-old children born very preterm in 2011. Two other studies have reported slightly lower prevalence rates of 2.6–3.6% in European and Australian children born very preterm/very low birth weight (Sellier et al., 2016; Smithers-Sheedy et al., 2022). However, the number of children with CP in this thesis was limited (n=9), preventing more comprehensive conclusions regarding the prevalence trends of CP in children born very preterm. Furthermore, the main aim of this thesis was to study aspects of neurodevelopmental impairments other than CP.

## 6.2 Neurodevelopment and quality of life at 11 years

### 6.2.1 Neurodevelopmental follow-up

In this thesis, a long-term follow-up was conducted to study the neurodevelopmental outcome, including the rates and co-occurence of neurological and motor impairments "milder than CP", and cognitive impairment, in early adolescence. In many research and clinical settings, the systematic follow-up of children born very preterm is conducted until 2 years of corrected age, since the most severe neurodevelopmental impairments can usually be detected by that time. However, long-term follow-up with a stronger focus on academic achievement is suggested. The European foundation for the care of newborn infants has recommended that e.g. neurological status and motor development, cognition, speech and language development, and behavior and attention should be assessed when transitioning to school. (EFCNI, 2018.)

### 6.2.2 Neuromotor outcome

When the rate of DCD is evaluated, gestational age status and the degree of prematurity should be considered. In this PIPARI study cohort, 11% of the children born very preterm had DCD i.e. motor impairment other than CP. To determine DCD we used a cut-off of the 5th percentile of the normative data of the Movement ABC-2. If a broader 15th percentile cut-off had been used, the rate of DCD would have been 19%. In the general pediatric population, the prevalence of DCD is estimated to range from 5% to 6%, whereas in children born preterm, an over-representation of DCD has been described (Blank et al., 2019; Williams et al., 2010). The DCD rate of this PIPARI cohort is in line with the report of the European Academy of Childhood Disability (EACD) (Blank et al., 2019).

In this thesis, all but one of the children with DCD were boys. This reflects the previous finding that, in addition to preterm birth, male sex is an important risk factor for DCD (Van Hoorn et al., 2021). However, the small number of children with DCD in this thesis did not enable comprehensive statistical analysis regarding sex. Of the other background characteristics, lower gestational age, bronchopulmonary dysplasia, sepsis, and major brain pathologies on an MRI at term were associated with DCD at 11 years of age. Considering the relationship between very preterm birth and DCD, the association of lower gestational age and DCD was expected. Further, our results are in line with other studies showing that postnatal corticosteroids and bronchopulmonary dysplasia associate with motor impairments and DCD (Cheong & Doyle, 2018; Van Hoorn et al., 2021). Although previous

findings regarding pathological neonatal brain MRI findings and DCD are contradictory, this thesis indicates that brain pathologies in a brain MRI at term are associated with subsequent DCD.

In this thesis, a higher, i.e. better, HINE score at 2 years was shown to associate with better motor outcome at 11 years. However, the association did not remain statistically significant when children with CP were excluded. This was an expected finding and supports previous study which has presented that a developmental assessment at 2 years of age may have low sensitivity for mild-to-moderate impairments in the absence of CP (Spittle et al., 2013). The HINE has shown to correlate with neonatal brain imaging findings and to have a 90% sensitivity for predicting CP (Haataja et al., 2001; Novak et al., 2017). An association between major brain pathologies on a neonatal MRI and subsequent DCD was observed in this thesis. Thus, more pronounced association between the HINE and DCD, even in the absence of CP, may have been assumed.

To identify DCD, a valid, reliable, and standardized motor method should be used (Blank et al., 2019). Currently, the Movement ABC-2 is reportedly the most frequently used method (Henderson et al., 2007), and was also used in the motor assessment of the very preterm cohort in this thesis. The selected assessment method and the cut-offs should be noted when comparing the prevalence rates of DCD. It has been reported that the rate of DCD in children born preterm ranged from 8–10 to 34–37 % when evaluated with a stricter cut-off criterion, such as the 5th percentile in the Movement ABC-2 or <-2 SD in the Bruininks–Oseretsky Test. The reported rate of DCD has varied from 12–22 up to 71–72% when evaluated with broader cut-offs, e.g. 15th percentile the Movement ABC-2 or <-1 SD in the Bruininks–Oseretsky Test. (Evensen et al., 2020; Williams et al., 2010.) In the latest recommendations by the EACD, a cut-off ≤15th percentile is recommended especially in clinical settings since the stricter cut-off criterion may miss the children with moderate DCD (Blank et al., 2019). In our study, we chose to apply the 5th percentile cut-off in the Movement ABC-2 because 1) according to the EACD, the scores ≤5th percentiles should be considered an unequivocal evidence of DCD; and 2) according to the Movement ABC-2 manual, the scores ≤5th percentile indicate motor difficulty while the scores >5th to 15th percentile indicate risk of movement difficulties (Henderson et al., 2007; Henderson & Sugden, 1992).

Another important aspect in the interpretation of the findings are the test norms which should be adjusted for different countries (Blank et al., 2019). Regarding studies of children born preterm, studies using cut-offs based on their own control group seem to identify greater prevalence of motor impairments other than CP compared to studies using normative cut-offs (Bolk et al., 2018; Williams et al., 2010). Therefore, it is recommended to report impairment rates according to both

local and normative cut-offs (Williams et al., 2010). In this thesis, normative cut-offs were used due to a lack of Finnish norms and an own control group.

It is recommended that when defining DCD, questionnaires should be used as a supplementary information but not as a diagnostic tool (Blank et al., 2019). There are several questionnaires available for the evaluation of motor function and detection of DCD. However, the sensitivity and specificity of these questionnaires have shown to be highly variable depending on the person completing the forms (child, parent, teacher etc) as well as the sample (study population vs clinical setting) (Blank et al., 2019). It has been shown that the parents seem to underestimate the children's motor difficulties (Bolk et al., 2018).

DCD interferes with daily tasks and activities, including writing, dressing and running. Furthermore, DCD is associated with difficulties across many areas including cognitive skills, language development, mathematical skills and mental health (Blank et al., 2019; Twilhaar et al., 2022). Consistently, this thesis showed that children born very preterm with DCD had poorer cognitive outcome compared to peers born very preterm without DCD. This finding was evident in general intelligence, measured with the full-scale IQ, as well as in all its' indexes including verbal comprehension, perceptual reasoning, working memory, and processing speed. The clinical relevance of this difference is noteworthy, since the mean full-scale IQ of the children with DCD was 15 points lower compared to the children without DCD.

The diagnosis of DCD is not recommended before 5 years of age, mostly due to the possible spontaneous catch up of motor skills (Blank et al., 2019). However, in children born very preterm and thus with an increased risk for DCD, motor impairment at 4 years has shown to be predictive for motor impairment at 8 years of age (Griffiths et al., 2017). In addition, poorer motor skills seem to persist from adolescence to adulthood in children born preterm with very low birth weight (Husby et al., 2013). The role of genetic factors in DCD will probably be of future interest since current findings suggest that there may be susceptibility genes for DCD (Blank et al., 2019). Mountford et al. (2021) have published a study reporting the first genes suggested to be associated with motor coordination in children. However, the research regarding the genetics of DCD is in its infancy and no specific genes have been identified as causative. To date, knowledge of the risk factors predictive for DCD, apart from preterm birth and male sex, has remained limited and studies of factors that might protect from DCD are lacking. More precise understanding of the etiology and risk factors of DCD is needed in the future.

In addition, this thesis showed that the children with DCD, compared to those with a typical motor outcome, had a lower self-experienced HRQoL. These findings may help to understand the clinical significance of DCD and underline the importance of the recognition of "milder" motor impairments even in the absence of

CP. Perceiving the adverse effects of DCD on activities of daily living, many children with DCD would benefit from interventions aimed at enhancing functioning, activity, and participation. Despite the emerging evidence of the possible positive effects of interventions in DCD, further studies are needed to determine the best-practice interventions for children with/at risk of DCD (Blank et al., 2019; Smits-Engelsman et al., 2018; Zwicker & Lee, 2021).

In this thesis, 80% of the 11-year-old children born very preterm without CP had a typical neurological outcome when evaluated according to the Touwen neurological examination. The category of a typical neurological outcome included both the children with a result that was neurologically typical and children with simple MND. An increase in the rate of simple MND has been described during the past decades, whereas the rate of complex MND has remained unchanged (Hadders-Algra, 2010). In the general pediatric population, the reported rate of simple MND has ranged from 20 to 23% and the rate of complex MND from 0 to 7% (Arnaud et al., 2007; Peters et al., 2011; Tommiska et al., 2020). Similar to DCD, children born preterm have shown to have an over-representation of MND compared to the general pediatric population. The simple MND rate of 41% in our cohort of children born very preterm was similar with the previously reported rates of 39% to 41% of simple MND in children born very/extremely preterm (Arnaud et al., 2007; Tommiska et al., 2020). The rate of complex MND in this thesis (20%) was higher compared to the complex MND rates of 3% and 13% reported by Arnaud et al., 2007 and Tommiska et al., 2020.

The age at the time of the assessment should be noted when the rates of MND are compared, since the rate of MND has been described to increase with age (Hadders-Algra, 2002). In addition, before puberty, the classification of a neurological outcome is based on number of the dysfunctional domains in the Touwen neurological examination; after the onset of puberty, the classification is determined by the type of dysfunction (Hadders-Algra, 2010). In this thesis, the classification of 11-year-old children was conducted by using the computerized scoring with prepubertal norms.

The fairly high rate of simple MND in this thesis is supported by previous literature (Hadders-Algra, 2010) suggesting that very preterm birth, even without perinatal risk factors, is associated with an increased risk for simple MND. Other risk factors for simple MND have remained largely indefinite. It has been proposed that simple MND represents typical albeit non-optimal functioning of the brain. In contrast, complex MND has been linked with morbidities and pathological brain findings during the neonatal period. (Hadders-Algra, 2010.)

To our knowledge, this is the first study to evaluate the association between the HINE and the long-term neurological outcome in middle-school age. In this thesis, it was shown that better performance in the HINE at 2 years was associated with a

better neurological outcome at 11 years. When the children with CP were excluded, this association did not remain statistically significant. However, children with a typical neurological outcome had a higher HINE posture subsection score compared to those with complex MND, even when the children with CP were excluded. It has been suggested that typical development of posture control is characterized by ability to adapt to the specific situations while atypically developing children may have difficulties in adapting postural control (Hadders-Algra, 2013).

Complex MND has been shown to associate with motor impairments such as DCD, cognitive adversities, learning difficulties, and behavioral problems in children born preterm and in the general population (Broström et al., 2018; Ferrari et al., 2012; Hadders-Algra, 2010). Consistently, it has been reported that the rate of complex MND was 53% in children attending special education, regardless of the gestational age (Peters et al., 2011). The co-occurence of complex MND and DCD was not studied in this thesis. Acknowledging previous literature, an overlap of these two deficits may have been suspected. In this cohort, complex MND was more prevalent than DCD (20% vs 11%). An explanation might be that although the children born very preterm performed within a typical level in the quantitative assessment to detect DCD (the Movement ABC-2), the challenges may have become more pronounced in the qualitative assessments such as Touwen neurological examination that was used to detect MND.

Both complex MND and DCD were associated with an adverse cognitive outcome based on the findings of the present thesis. The full-scale IQs of the children with DCD or complex MND were 14.8 points and 10.6 points lower than the full-scale IQ of the children with a typical motor or neurological outcome, representing clinically significant difference. The children with complex MND had a poorer general intelligence compared to their peers with a typical neurological outcome. The rate of severe cognitive impairment i.e. full-scale IQ<70 was as high as 26% in 11-year-olds born very preterm with complex MND. In contrast, the rate of severe cognitive impairment was only 3% in children born very preterm with a typical neurological outcome. The high rate of severe cognitive impairment in children with complex MND underlines not only the clinical relevance of complex MND but also the importance of its early detection and targeted support services.

### 6.2.3 Cognitive outcome

This thesis showed that 8% of the 11-year-old children born very preterm without CP had severe cognitive impairment defined as full-scale IQ<70. Of those with CP, 56% had severe cognitive impairment. By comparison, a Finnish national register study including all live-born children from 1991 to 2008 reported that 0.4% of 7-year-old children born at term and 2.5% of 7-year-olds born very preterm had severe

cognitive impairment (full-scale IQ<70) and significant limitation in adaptive functioning (Hirvonen et al., 2017). Severe cognitive impairment was shown to associate with DCD and complex MND, even when the children with CP were excluded. In this population of 11-year-old children born very preterm, 58% of those with severe cognitive impairment had concurrent DCD and 67% had complex MND.

A variety of possible risk factors for adverse cognitive outcome have been studied. Lower birth weight, male sex, non-white race/ethnicity and lower paternal education have been shown to be prognostic for an adverse cognitive outcome in children younger that 5 years, but only the influence of paternal education has been shown to be sustained into childhood (Linsell et al., 2015). The role of brain pathologies to cognitive development has been debated. On the one hand, a major brain pathology was shown to be a risk factor for an adverse cognitive outcome (Nyman et al., 2017) based on previous findings of this PIPARI study population. While, on the other hand, according to a systematic review, the prognostic value of brain pathologies to cognitive development was shown to be variable (Linsell et al., 2015). A reason for this may be that there are multiple factors affecting cognitive development and it seems not as directly related to brain injury as for instance CP (Linsell et al., 2015). In addition, the influence of perinatal risk factors appears to diminish and the role of environmental factors, e.g. parental education, become more pronounced during childhood in children born very preterm or with very low birth weight (Linsell et al., 2015).

Neurological assessment at term has been shown to associate with cognitive development at 2 years in children born preterm (Spittle et al., 2017b). Hack et al. (2005) have reported a poor predictive validity of a cognitive assessment at 2 years for later cognitive outcomes. It has also been suggested that the results of developmental tests performed before or around 2 years underestimate the rate of subsequent cognitive impairments (Pascal et al., 2018). Nonetheless, a good stability of cognitive development in children born very preterm from 2 to 5 years, and 5 to 11 years has also been reported (Munck et al., 2012; Nyman et al., 2017). However, the IQ scores of the children with a low IQ at a preschool age have reported to be more stable compared to the IQ scores of the children with an average or high IQ. From 12 to 14 years onwards intelligence does not appear to go through major changes. (Schneider et al., 2014.)

This thesis showed an association between the results of neurological examination (the HINE) at 2 years and general intelligence assessed 9 years later. When the HINE global score, assessed at 2 years, increased by 1 point, the subsequent full-scale IQ, assessed at 11 years, was improved by 1.2 points. Recent studies of children born preterm and full-term have shown that the HINE assessments between 3 and 12 months of corrected age can help to identify children

with a high risk for not only CP but also for significant cognitive delay without CP at 2 year of age. These studies have also shown correlation between the HINE global scores at 3, 6, 9 and 12 months of corrected age and cognitive delay at 2 years of corrected age, with a stronger correlation from 6 months onwards. (Romeo et al., 2020, 2022.)

To evaluate the association between the HINE at 2 years of corrected age and the neurodevelopmental outcome at 11 years, we used the HINE as a continuous variable instead of setting cut-offs. The ROC analysis conducted in this thesis showed that the HINE had an acceptable ability in distinguishing children with and without severe cognitive impairment at 11 years, but this ability was reduced when children with CP were excluded. Since publishing the articles included in this thesis, Romeo et al. (2020, 2022) have identified specific cut-off scores for the HINE that could help to identify 3, 6, 9, and 12 months old infants with normal outcomes from those with neurodevelopmental impairments at 2 years of age. Their results support the findings of this thesis showing that the HINE may help to detect children at risk for later neurodevelopmental disabilities (also other than CP) up to middle-school age. It is important that the cut-off scores are not used in isolation but interpreted simultaneously with other clinical findings and brain imaging data.

In this thesis, severe cognitive impairment was more common in children with DCD or complex MND compared to peers without these impairments. The WISC-IV has few items in the processing speed and in the perceptual reasoning index subtests that require fine motor control (eg, holding a pen, drawing in a small space and manipulating blocks). It is possible that the concurrent DCD and/or complex MND may have affected on the child's performance in these subtests. However, children without DCD or complex MND also had better performances in both indexes of verbal comprehension and working memory, which do not require fine motor control, compared to the children with DCD or complex MND.

### 6.2.4 Self-experienced health-related quality of life

This thesis showed that 11-year-old children born very preterm in the 2000s had a better self-experienced HRQoL compared to same age normative population based on the same age Finnish children who had completed the 17D before 1996. This was an unexpected finding, since this thesis also showed that children born very preterm have an increased risk for neurodevelopmental impairments which in turn might lower their HRQoL. Although the findings of a better self-experienced HRQoL compared with norms was not hypothesized, the finding of good self-experienced HRQoL in this very preterm study population reflects earlier studies (Huhtala et al., 2016; Natalucci et al., 2017). Huhtala et al. (2016) have shown that at nearly 8 years

the self-experienced HRQoL of the PIPARI study children born very preterm without neonatal morbidities was similar to the controls in the PIPARI study born at term. 31-year-old adults born preterm between 24 and 36 weeks of gestation have reported an HRQoL, assessed with the Australian version of the Short Form-36 Health Survey, that was similar or better when compared to control adults born at term (Dalziel et al., 2007). In this thesis, the mothers of the study children had a higher educational level compared to the mothers of the children who withdrew. This drop-out effect may have influenced the results regarding self-experienced HRQoL.

The effect of preterm birth and/or very low birth weight on HRQoL seems to be most significant in younger years and seems to decrease over time. This finding might be influenced by the effect of self-reporting versus parent-reporting since it has been suggested that parents of very/extremely low birth weight teenagers perceive their child's HRQoL lower than the teens themselves. (Zwicker & Harris, 2008). The multinational European study of 5-year-olds born very preterm showed that the parental-measured HRQoL was particularly affected by extremely preterm birth (<28 weeks of gestation) and severe neonatal morbidities (Kim et al., 2022). Earlier findings from the PIPARI study have shown that 8-year-old children born very preterm with neonatal morbidities had lower self-experienced HRQoL compared to peers born very preterm without neonatal morbidities (Huhtala et al., 2016) suggesting that the the effect of these early morbidities on HRQoL persists into school-age. Natalucci et al. (2017) have reported that surgical closure of patent ductus arteriosus affected both self- and parent reported HRQoL of Swiss 12-year-olds born very preterm.

It has been suggested that children (aged 8 to 12 years) with DCD experience a lower HRQoL than their peers (Karras et al., 2018). Another study reported that children with DCD do not display poorer overall HRQoL compared to typically developing children; however, the adolescents with DCD and concurrent ADHD showed a lower HRQoL compared to typically developing peers (Dewey & Volkovinskaia, 2018). These studies by Karras et al. and Dewey & Volkovinskaia evaluated the association between the HRQoL and DCD, irrespective of the gestational age/birth weight status. This may be an important detail, since it has been shown that functional outcomes, including cognitive abilities, CP, hearing and visual impairments and emotional problems, are indicative of HRQoL in children born very preterm but not in peers born full-term (Wolke et al., 2013).

In this thesis, no difference was found between the self-experienced HRQoL of children born very preterm with and without CP or the children with and without severe cognitive impairment. However, the results also indicated that children born very preterm with DCD had a lower self-experienced HRQoL compared to children born very preterm with a typical motor outcome in early adolescence. This is in interesting finding suggesting that DCD, commonly denoted as a "mild" impairment,

seems to have a stronger effect on self-experienced HRQoL compared to the severe motor impairment, ie CP, and severe cognitive impairment. Considering the adverse effects of DCD on activities of daily living, this finding seems reasonable. In children with DCD, the affected domains were vision, hearing and speech. Nevertheless, the absolute differences in self-experienced HRQoL were minor since the scoring system only ranges from 0 to 1. Whether these statistically significant differences have a clinical importance is not definite.

## 6.3 Hand coordination skills at 13 years

The thesis includes a comparison of the hand coordination skills and concurrent brain fMRI findings between the 13-year-old adolescents born very preterm and controls born full-term. We hypothesized that the hand coordination skills would be poorer in adolescents born very preterm compared to the control adolescents. Unexpectedly, adolescents born very preterm performed within the same level in hand coordination tasks compared with the controls. The assessment of hand coordination skills at 13 years included finger opposition and diadochokinesis. These two tasks were chosen since it has been suggested that dysfunctions in fine manipulative and coordination skills have the most significant clinical importance. Both these skills require and reflect the functioning of complex supraspinal circuitries. Moreover, of all the Touwen neurological examination domains, the fine manipulative and coordination skills are most strongly shown to associate with motor, learning, and psychiatric outcomes. (Hadders-Algra, 2010.)

The performance of finger opposition and diadochokinesis was evaluated according to the classification criteria of the Touwen neurological examination (Hadders-Algra, 2010). The evaluation of finger opposition included evaluation of finger-to-finger transition and smoothness of the movement. Regarding the performance of diadochokinesis, regularity and speed of the movement were evaluated, and in both tasks, the associated movements of the contralateral hand were assessed. No difference in the rates of hand coordination dysfunction between adolescents born very preterm and controls was found. Regarding the performance of finger opposition, the rate of dysfunction in the very preterm group was only 3% and none of the control adolescents had dysfunctions. The rate of dysfunctional performance in diadochokinesis was 6% in the very preterm adolescents and 0%/3% (right hand/left hand) in controls. This finding is different from the previously reported rates of 16% to 20% of fine motor impairments (defined as manual dexterity <5th percentile on standardized test) in children born very preterm (Bos et al., 2013; Evensen et al., 2009). The results of Husby et al. (2013), which suggested that the fine motor performance of young adults born very preterm is accurate albeit slower than that of controls born at term, are in line with the findings of this thesis.

This thesis showed a high rate of associated movements of the contralateral hand both in the very preterm group and in the controls indicating that nonoptimal performance in associated movements during hand coordination tasks is common regardless of the gestational age. It has been reported that the prevalence of coordination dysfunctions has risen during the past decades, and that fine motor skills seems to fall below the expected levels compared with normative data (Gaul & Issartel, 2016; Hadders-Algra, 2010). Additionally, more complex tasks have been reported to associate with increased associated activity (Hadders-Algra, 2010). Fine motor tasks have a significant role during the school-day and fine motor impairment adversely affects academic achievement as well as leisure activities and participation. Therefore, it is essential to study not only the rates of fine motor impairment but also the cause of the increased rates of non-optimal hand coordination performance.

## 6.4 Functional magnetic resonance imaging findings at 13 years

The fMRI was performed during the hand coordination tasks and the brain activation was compared between adolescents born very preterm and controls born full-term. Each hand coordination task induced an activation pattern that showed similarity in the location of the activated areas; the most activated areas in both the adolescents born very preterm and controls were the contralateral primary sensorimotor cortex, the bilateral medial and lateral premotor areas, and a part of the cerebellum. These areas show a resemblance to brain areas that have been reported to associate with finger-tapping tasks in adults (Witt et al., 2008). In addition, the adolescents participating this thesis showed some activation in the occipital cortex. This may have occurred due to the visual difference between the cues used to address the alternation of the hand coordination task and gaze fixation periods. In line with a previous study by Lawrence et al. (2014), this thesis showed that the activation was stronger in adolescents born very preterm compared to peers born full-term as hypothesized. The activation difference was always located in the contralateral primary sensorimotor hand area. Within the adolescents born very preterm, the cerebellar and superior parietal activations were found to associate with gestational age.

The fMRI findings of this thesis showed that the participants born very preterm had stronger activation in the contralateral primary sensorimotor cortex during non-dominant left-hand coordination tasks compared to controls born at term. The finding of activation difference only during the left-hand tasks may be explained by decreased efficiency of motor control and related excessive neural activation for the non-dominant hand in adolescents born very preterm, while for dominant right hand

such difference could have already diminished by the age of 13. Moreover, the activation difference was only found in the primary sensorimotor cortex but not in the premotor areas.

The clinical performance of hand coordination tasks was similar in adolescents born very preterm and controls despite the activation differences. It has been suggested that in more difficult tasks, when the capacity of certain brain area is reached, additional brain areas could participate in order to manage the task (Just & Varma, 2007). Thus, the excessive activation in participants born very preterm might be a compensatory mechanism that helps to achieve the optimal clinical performance and explain the findings of this thesis. Lawrence et al. (2014) studied brain activation in fMRI during dominant hand motor task in which they had been instructed to move a joystick once, in a randomly chosen direction, as quickly as possible when visual stimuli was shown. They reported that although 20-year-olds born very preterm had clinically similar motor task performance compared to controls, the participants born very preterm had greater brain activation in fMRI during the motor task although the areas in which the increased brain activation was detected were in the right-sided cerebellum, and the lingual, parahippocampal and middle temporal gyri (Lawrence et al., 2014). In this thesis, the between-group comparisons of adolescents born very preterm and controls showed no activation differences in the cerebellum. This alteration may be due to differences in the motor tasks evaluated and in the brain areas covered between the study by Lawrence et al and this thesis.

Within the group of adolescents born very preterm, the cerebellar and superior parietal activations were influenced by gestational age. During finger opposition of the left hand, lower gestational age was associated with stronger activation, revealing a negative dependence between anterior cerebellar activation and gestational age. Motor control of the non-dominant left hand in right-handed individuals might require more resources compared to motor control of the dominant, i.e. the right hand. This effect appeared to increase as gestational age decreased. Similar negative dependence between right superior parietal lobule and gestational age was detected during the diadochokinesis of the left hand. However, limited data is available regarding the brain activation differences between children/adolescents born very preterm and controls born at term. Comprehensive comparison between the results of this thesis and previous studies is therefore challenging.

Unexpectedly, for the right hand diadochokinesis, a positive dependence between the activation of the left superior parietal lobule and gestational age was found, demonstrating that the activation decreased with decreasing gestational age. A previus study has shown that children with DCD had reduced activation during manual dexterity tasks in the middle frontal gyrus, superior frontal gyrus, cerebellum, supramarginal gyrus, and inferior parietal lobule (Fuelscher et al., 2018). In this thesis, the number of adolescents with dysfunctions in hand coordination tasks

were small and did not enable more comprehensive analysis regarding the combined effect of hand coordination skills, gestational age and brain activation findings. Further research is needed to study whether the decreased activation in more premature born adolescents reflects the increased susceptibility for dysfunctions in hand coordination tasks and even for DCD. Overall, these findings may reflect compensatory neural mechanisms in adolescents born very preterm, that enable appropriate hand coordination performance compared with adolescents born at term. The results of this thesis demonstrate the potential of fMRI to detect long-lasting neural mechanisms after very preterm birth even in cases in which they cannot be determined by clinical assessment methods.

## 6.5 Strengths and limitations

The strength of this thesis is that it is a longitudinal prospective cohort study. At 11 years especially, the follow-up rate was reasonably high, almost 80%. All neurodevelopmental assessments at 11 years were conducted using the latest full versions instead of abbreviated measures. To assess the cognitive outcome and to define severe cognitive impairment, the WISC-IV with up-to-date Finnish norms was used. At 13 years, all clinical examinations were video recorded and scored together with an experienced child neurologist to guarantee the analogy between the hand coordination task assessments. In addition, both the clinical examination of the hand coordination tasks and concurrent in-scanner fMRI data during these tasks were available.

There are also limitations to this thesis. The results were based on a single-centre study population with relatively small subgroups of children with adverse outcomes, which may limit the generalizability of the findings. There was no possibility to compare the neurodevelopmental outcomes to peers due to the lack of a control group. An additional possible limitation was that the Movement ABC-2 was not performed repeatedly as suggested in the latest EACD recommendations (Blank et al., 2019). In addition, the Movement ABC-2 and the Touwen neurological examination were carried out by the same assessor, causing a risk for potential bias that could have been associated with the order in which the assessments were applied (first the Movement ABC-2 which is a quantitative assessment, second the Touwen neurological examination which is based on the assessor's qualification). To minimize the risk of this kind of bias all the Movement ABC-2 and Touwen assessments were video recorded and reassessed together with an experienced child neurologist (LH) in case of any hesitation regarding the examinations. Regarding the self-experienced HRQoL, the Finnish norms of the same age population were available, but the norms were based on data collected before 1996. At 13 years, only right-handed adolescents were included to minimize the effect of handedness,

however, the handedness was based on self-reported information instead of performance measures. Moreover, scoring of the hand coordination tasks was performed outside the scanner before the fMRI and although the accomplishment of these tasks was monitored during the in-scanner session, the performance was not repeatedly scored. This is however a fairly standard setting in fMRI, and not likely of significant importance for drawing conclusions.

## 6.6 Future perspective and clinical implications

The ultimate goals in the care of children born very preterm are to identify the women at risk for very preterm birth and to prevent these premature births. While aiming to accomplish this, more research is needed to further improve treatments and interventions that help to prevent the adversities related to very preterm birth.

This thesis has demonstrated that the HINE can aid early detection of children born very preterm with an increased risk for cognitive impairment at 11 years. These findings highlight that the HINE may be used to detect not only CP but also children with an increased risk for subsequent cognitive impairment. The clinical usability of the HINE, including the cut-offs at different ages, needs to be further explored in future studies. More advanced MRI-technologies such as diffusion MRI-based connectivity analyses could further elucidate the functional and likely compensatory changes observed.

This thesis showed that the children born very preterm had an increased risk for an adverse outcome regarding motor, neurological and cognitive outcomes at middle-school age, even in the absence of CP. Based on the finding of this thesis, children born very preterm may benefit from long-term follow-up lasting until early adolescence. This would enable the early recognition of neurodevelopmental impairments and the initiation of appropriate targeted support services to optimize neurodevelopment.

# 7 Summary/Conclusions

In this thesis, the long-term neurodevelopmental i.e. neurological, motor, and cognitive outcomes, and self-experienced health-related quality of life of children born very preterm was evaluated at 11 years of age. The association of neurological examination at 2 years of corrected age and neurodevelopmental outcomes at 11 years of age was assessed. In addition, the performance of hand coordination tasks and the brain activation in functional magnetic resonance imaging (fMRI) during these tasks were evaluated at 13 years, and the results were compared between the adolescents born very preterm and controls born full-term.

This thesis presents the following conclusions:

1. The Hammersmith Infant Neurological Examination (HINE) performed at 2 years was associated with the cognitive outcome at middle-school age in children born very preterm.
2. The majority of the children born very preterm had a typical neurodevelopmental outcome at 11 years of age. Children with developmental coordination disorder (DCD) or complex minor neurological dysfunction (MND) had a significantly higher rate of severe cognitive impairment compared to peers born very preterm without DCD/complex MND.
3. The overall self-experienced health-related quality of life (HRQoL) in 11-year-olds born very preterm was good.
4. The hand coordination skills of 13-year-old adolescents born very preterm did not differ from the same skills demonstrated by controls born full-term. However, adolescents born very preterm had stronger activation in the contralateral primary sensorimotor cortex during left-hand coordination tasks compared to controls in fMRI at 13 years. Within the group of adolescents born very preterm, the cerebellar and superior parietal activations were influenced by the gestational age.

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