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

NEUROMOTOR DEVELOPMENT AND BRAIN STRUCTURE IN CHILDREN BORN EXTREMELY PRETERM

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Karolinska Institutet

Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-788-8
Cover illustration: Miranda Broström Norén 10 years old and born preterm

NEUROMOTOR DEVELOPMENT AND BRAIN STRUCTURE IN CHILDREN BORN EXTREMELY PRETERM
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Atrium, Nobels väg 12 B, Wargentinhuset,Stockholm, 14th of December 2022 at 9 a.m.

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To my family

POPULAR SCIENCE SUMMARY OF THE THESIS

Does being born too early mean problems at school age?

Vera had been in preschool for four months when her teachers and her parents realized that something was not right. She found it difficult to keep up with her peers and concentrate and had problems learning letters. She didn't want to take part in sports at school, because she did not feel she could do what her classmates were able to do. What Vera's parents knew, but the teachers were unaware of, was that Vera was born about three months early.

In the year 2021, 328 babies, like Vera, were born in Sweden about three months early[1]. Many children who are born prematurely have difficulties at school age compared to children born at full term. They can find it difficult to sit still, read, do mathematics, and carry out tasks that involve motor skills.

If we can predict which children face high risks of future problems, by examining them in infancy, we can provide special tailor-made follow-up programmes that address different risks. The aim is to recognize their difficulties at an early stage and ultimately intervene early. These children are born during a sensitive period of their brain development and by investigating how these changes in their brain relate to how they do later in life, we can identify the children who will need extra support. There is still a lot of work to be done to know what happens to children's development after extremely preterm birth. As a society we have a responsibility, to support children who are born extremely early.

Vera and her parents were lucky. The teachers at her school were eager to help her as much as they could, by providing support during lessons and extra private lessons in sports so that she could practice her motor skills. However, many of the children who are born extremely preterm find that their problems are too subtle for special schools, but too complex to deal with for mainstream schools. This means that they find themselves in a grey area and do not get the help they need.

ABSTRACT

Children born extremely preterm (EPT) are increasingly surviving but it is well known that they face a high risk of brain injury and neurodevelopmental impairments. The overall aim of the studies included in this thesis was to investigate the relationships between brain alterations and neurodevelopment, with specific focus on neuromotor outcomes in children born EPT.

The children that took part in these studies were born in Sweden before 27 weeks of gestation, between 1 January 2004 and 31 March 2007. When they reached term equivalent age they underwent a magnetic resonance imaging (MRI) scan of their brain, and this was repeated at 10 years of age. Neurodevelopmental assessments were carried out at 6.5 and 12 years of age. Matched controls also underwent MRI scans at 10 years of age and the 2 developmental assessments at 6.5 and 12 years of age. These were recruited from the Swedish Medical Birth Registry and matched with for postcode, age, maternal country of origin, and sex.

Study I found subtle white matter changes on the MRI brain scans at term age in 59% of the 66 children born EPT who had MRI. There were no significant differences in neurodevelopmental outcomes at 6.5 years of age between the EPT children with and without subtle white matter changes.

Study II found that the prevalence of minor neurological dysfunction (MND) was higher in children born EPT than in the term-born control group at 6.5 years of age. MND was associated with motor skills and cognitive abilities.

Study III found that children born EPT had significantly smaller regional volumes of the thalamus, the basal ganglia, volumes of structures involved in the brains motor network and the cerebellum than the term-born controls at 10 years of age. EPT-born children with definite motor impairment (≤5 centile) in the subtest of ball skills of the Movement Assessment Battery for Children, Second Edition (MABC-2) at 12 years of age had significantly smaller volumes of the basal ganglia, volumes of structures involved in the brains motor network and the cerebellum than EPT-born children without these problems.

Study IV found that the children born EPT with a low-grade intraventricular haemorrhage (IVH) did not have smaller volumes of white or grey matter in the cerebrum or cerebellum at 10 years of age than the EPT children without low-grade IVH. We did not find any differences in motor skills cognitive abilities or visual motor integration between these two groups.

The children born EPT with subtle white matter changes on their MRI scans at term age, or low-grade IVH on their cranial ultrasounds, did not have more neurodevelopmental problems in late childhood than the EPT-born children without these findings. This could possibly be reassuring when discussing such findings with parents of children born EPT. However, children born EPT had worse neurological profiles, with higher prevalence of MND than their term-term peers at 6.5 years of age and these were related to motor skills and cognitive function. The EPT-born children with poorer performance on one of the MABC-2 subtests,

ball skills, at 12 years of age had smaller brain volumes than the EPT-born children who did not have these issues. This highlights the importance of follow-up visits and interventions after EPT birth.

LIST OF SCIENTIFIC PAPERS

I. **Lina Broström***, Jenny Bolk*, Nelly Padilla, Beatrice Skiöld, Eva Eklöf, Gustaf Mårtensson, Brigitte Vollmer, Ulrika Ådén. Clinical Implications of Diffuse Excessive High Signal Intensity (DEHSI) on Neonatal MRI in School Age Children Born Extremely Preterm. *PlosOne* 2016 Feb 17, ISSN:1932-6203 Volume:11 Issue:2 Pages:e0149578

*These authors contributed equally to this work

II. **Lina Broström***, Brigitte Vollmer*, Jenny Bolk, Eva Eklöf, Ulrika Ådén. Minor neurological dysfunction and associations with motor function, general cognitive abilities, and behaviour in children born extremely preterm. Developmental Medicine & Child Neurology. 2018 Aug;60(8):826-832

*These authors contributed equally to this work

III. **Lina Broström**, Hedvig Kvanta, Maria Örtqvist, Nelly Padilla, Ulrika Ådén. Reduced volumes in brain motor areas are related to impaired complex motor skills in children born extremely preterm at late childhood. *Manuscript*

IV. **Lina Broström**, Lexuri Fernández de Gamarra-Oca, Hedvig Kvanta, Maria Örtqvist, Nelly Padilla, Ulrika Ådén. Low-grade intraventricular haemorrhage, cerebellar growth and neurodevelopment when children born extremely preterm reach late childhood. *Manuscript*

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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary Dysplasia
CP	Cerebral Palsy
DCD	Developmental Coordination Disorder
DEHSI	Diffuse excessive high signal intensity
EPT	Extremely preterm
EXPRESS	Extremely Preterm Infants in Sweden Study
FTF	Five to Fifteen questionnaire
GMFCS	Gross Motor Function Classification System
IVH	Intraventricular haemorrhage
IQ	Intelligence quotient
MABC	Movement Assessment Battery for Children
MND	Minor neurological dysfunction
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NDI	Neurodevelopmental impairment
PDA	Patent ductus arteriosus
PVL	Periventricular leukomalacia
ROP	Retinopathy of prematurity
SDQ	Strength and Difficulties Questionnaire
VMI	Visual-Motor Integration
WISC	Wechsler Intelligence Scale for Children
WMA	White matter abnormality

1 INTRODUCTION

Children born before 28 weeks of gestation are classified as extremely preterm (EPT), Survival near the border of viability has improved significantly with the development of neonatal intensive care [2]. Morbidities such as necrotizing enterocolitis (NEC), septicaemia, circulatory disturbances, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) are common in children born EPT [3,4] and these morbidities have been associated with brain development and long-term neurodevelopmental outcomes [5-8]. Children born EPT are born during a vulnerable time of brain development and the immature brain are fragile and fluctuations of the blood flow, ischaemia and inflammation may lead to brain injury. These include white matter and grey matter injuries like diffuse white matter injuries, cystic periventricular leukomalacia (PVL) and intraventricular haemorrhages (IVH) [9].

There are risks for neurodevelopmental impairments (NDI), such as motor, cognitive and behavioural problems, in these children [10]. Around 10-41% of children born EPT have moderate and severe intellectual disabilities in childhood [11] and 20-37% are affected by motor impairment [12].

The use of advanced MRI techniques has made it possible to study alterations in brain development in preterm populations that can not be identified on radiological assessment. Volumetric measurements performed at term age have shown global and regional differences in brain volumes between preterm and term groups [13].

Severe white matter abnormalities in the brain and severe IVH have been associated with neurodevelopmental impairments in children born EPT [14,15]. However, knowledge is still lacking on the influence of subtle white matter changes and low-grade IVH on the neurodevelopment in these children.

To summarize, children born near the limit of viability are often affected by morbidities, brain injuries, subsequent altered brain development, and neurodevelopmental impairment. It is important to follow up these children after the neonatal period to see how their brain and neuromotor function continue to develop later in life.

2 LITERATURE REVIEW

2.1 Preterm birth

Preterm birth is defined as delivery before 37 weeks of gestational age; moderate to late preterm birth between 32 to <37 weeks, very preterm birth between 28 and 31 weeks and EPT birth before 28 weeks of gestation [2]. About 33 % preterm birth occurs due to identifiable complications with the baby or mother, and the rest occur spontaneously [16].

Nine to 12 % percent of children around the world are born preterm [2] and each year about 600.000 of them are born EPT [17]. In 2021, in Sweden 328 children were born EPT [1]. Between 2017-2021, the survival rates in Sweden were: 22 weeks (39%), 23 weeks (64%), 24 weeks (72%), 25 weeks (84%), 26 weeks (92%) and 27 weeks (92%) [1].

2.2 Neonatal morbidities after preterm birth

Neonatal morbidities of infants born preterm increases with decreasing gestational age [18,19]. The following section focuses on data of morbidity from Sweden and the Swedish national study Extremely Preterm Infants in Sweden Study (EXPRESS) [20].

The ductus arteriosus normally closes within 48 hours of birth in term-born children. It is common for the ductus to remain open in children born preterm, and treatment with ibuprofen, paracetamol, or surgical ligation may be needed due to the effect that PDA has on the child's circulation [21]. In the study EXPRESS, 61% of 497 children born before 27 weeks of gestation developed PDA [20]. Previous data from our group indicate that surgical treatment of PDA is one of the most important risk factors for impaired brain development in children born EPT [22].

Neonatal sepsis is common in children born preterm and this affected 41% of the children in the EXPRESS study [20]. Possible reasons include an immature immune system and invasive procedures that expose children to bacteria. Neonatal sepsis and inflammation have been related to mortality and have also been linked to a reduced volume of the brain, for example in the cerebellum [23].

ROP, which is when the retina is scarred by abnormal vascularization in the eye, is a common complication in children born preterm. The vessels in the eyes are not fully developed when a child is born preterm and they are sensitive to external stress, such as treatment with supplementary oxygen [24]. Studies have shown that 34% of children born preterm develop severe ROP [20], which may lead to visual impairment and even blindness [24]. The volumes of the brainstem and cerebellum at term age have been found to be altered in children with ROP and children treated for ROP have higher risk of neurodevelopmental impairment [25].

NEC has been reported in 6% of children born EPT [20]. The aetiology and pathophysiology of NEC is not clear, but 90 % of those that are affected are children born preterm. NEC is characterised by blood in the faeces, ileus and abdominal distension [24]. Altered white matter microstructure of the brain has been found in children with NEC [26 27].

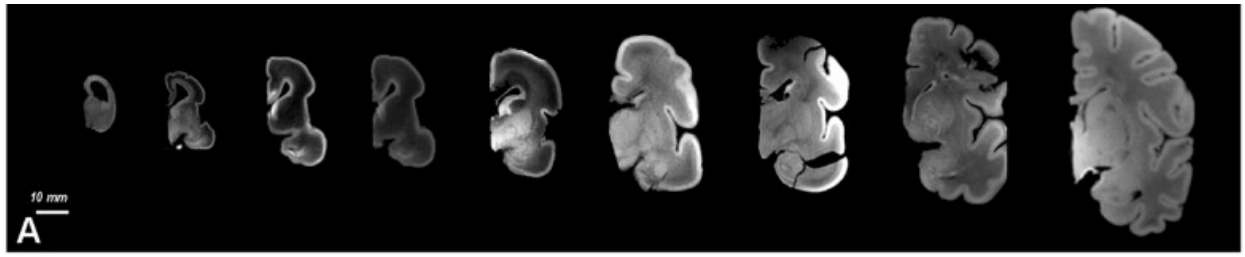
Respiratory problems are common in children born preterm and occur in nearly all children born EPT. The most common problems caused by immature lungs are respiratory distress syndrome and chronic inflammation and injuries from mechanical ventilation causing BPD. The definition of BPD is the need for supplementary oxygen at 28 days [28]. The incidence of BPD diagnoses in children born EPT has been reported between 48-68 % [29]. BPD has been identified as a risk factor for altered microstructure in the cerebellum, corpus callosum, corticospinal tract and smaller cerebral volume in the brain at term age [30].

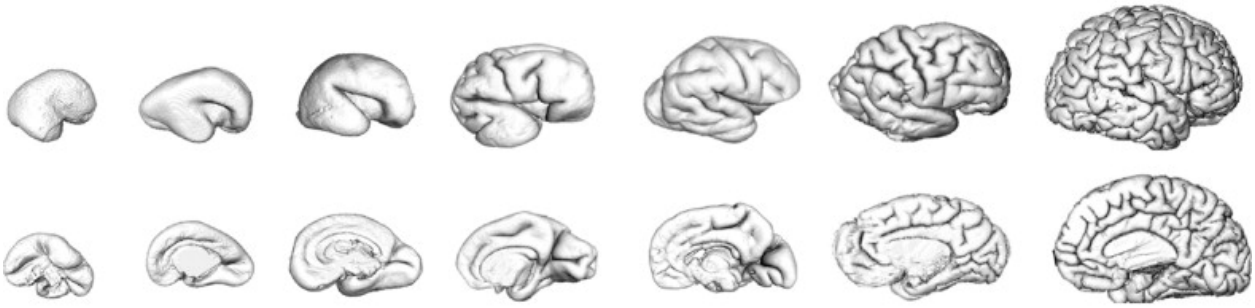
Altogether, there is evidence that the above mentioned perinatal and neonatal morbidities, independently of gestational age at birth, are related to brain development in children born EPT.

2.3 Brain development

After three weeks of conception, the gastrulation takes place from the three-layer oval shaped embryo. During this phase cell differentiation occurs, neural progenitor cells differentiate from the first layer of the embryo, from the epiblast cells, and eventually develop the cells of the brain [31]. Brain development starts with the formation of the neural tube, and is influenced by a number of environmental, genetical and biochemical processes [32,33]. The neural progenitors are located in the centre of the neural tube and this region will expand and eventually form the ventricular zone. The neural tube then expands and forms five brain vesicles that will transform into the central nervous system. Between ten and 20 weeks of gestation, the neural progenitors generate new neurons at a high speed. The neurons then radially migrate from the ventricular zone to develop the neocortex (six layers). The interneurons migrate tangentially in the region of the ventral telencephalon [34,35,31].

Once the neurons have migrated and reached their final position, they start to differentiate and build networks with other neurons. Axons, dendrites, and synapses start to develop at around 20 weeks of gestation. Programmed cell death also starts to take place around at 25 weeks of gestation. The subplate is formed below the neocortex, where afferent fibres from the brain stem and the spinal cord wait before they grow into the cortical plate. At 20-23 weeks of gestation, the afferent thalamocortical fibres gather in the subplate zone. Around 24-32 weeks of gestation the thalamocortical fibres grow into the cortical plate and the synaptogenesis starts. These pathways are very important for proper sensory signalling from the peripheral sensory receptors, through the thalamus and up to the cortex [31,35,34]. The oligodendrocytes, which are a subtype of glial cells, myelinate the axons and increase conduction, which is essential for efficient signalling between the neurons [36].





Mid/late fetal phase (15-23PCW)				Late preterm phase (33-35 PCW)	
Early fetal phase (9-13PCW)		Early preterm phase (24-32 PCW)			Near term phase (>36 PCW)
Parietooccipital fissure	Central sulcus	Precentral sulcus		Secondary sulci	Tertiary sulci
Olfactory sulcus	Superior temporal sulcus	Postcentral sulcus			
Cingulate sulcus		Parietal sulci			
Calcarine fissure		Superior frontal sulcus			
Callosal sulcus		Inferior frontal sulcus			
Sylvian fissure		Inferior temporal sulcus			

Figure 1. The developing foetal brain from 9-40 postconceptional weeks [34] Reprinted from Semin Perinatol 2009; 33: 220-33. Kostovic I, Vasung L. Insights from in vitro fetal magnetic resonance imaging of cerebral development. Copyright (2022), with permission from Elsevier

Development of the gyri and sulci (Figure 1*)* in the brain is an ongoing process from 15-23 weeks of gestation [34]. Around 33-34 weeks of gestation, the activity in the subplate decreases and is replaced by the cortico-cortical pathways growing into the cortex by [34,35,31].

At around 4 weeks after conception the cerebellum starts to develop from the hindbrain [32]. From 9 weeks to postnatal age around 7 months the cerebellum develops from two proliferation zones. From the ventricular zone the cells of granular layer and molecular layer, Purkinje cells and neurones of the deep nuclei, whereas the cells of external granular layer and deep nuclei develop from the rhombic lip. The cells of external granular layer also migrate to form the internal granular layer. Between 24 and 40 weeks of gestation the cerebellum increases five fold in volume with especially high proliferation of cells in the external granular layer also to form the internal granular layer. After around 40 weeks the external granular layer decreases in expansion with increase in the other layers of the cortex. The cerebellum then consists of 3 layers-cortex, white matter and deep nuclei. The cortex has three layers-granular cells that interact with cerebrum and middle layer with Purkinje cells and outer layer, the molecular layer. The vast majority of the cells of the cerebellum are granule cells [37].

2.4 Brain injuries in children born EPT

It is important to acknowledge the brain as a whole complex system with interactions and networks and not only specific regions that subserve with specific functions [38]. It has been described how supratentorial injuries also affect cerebellar growth and function and vice versa [9].

The children born EPT are born when the brain is undergoing important development, the preterm brain is therefore vulnerable [39] and injuries including IVH, cystic PVL, diffuse white matter injuries, grey matter injury and cerebellar injury are common in these children. This is often associated with disruption of normal brain growth and brain development [9]. Even in the absence of overt injury, the preterm brain is at work for poorer growth and development [40,9].

2.4.1 IVH

The germinal matrix is located on the surface of the lateral ventricles, and has a rich, but immature, vascular system. Cerebral blood flow fluctuations, inflammation and vascular factors may lead to vascular bleeding and blood may spread from the germinal matrix to the lateral ventricle [41]. Papile et al [42] graded the severity of IVH depending on the location and extent of the bleeding. Grade I is a haemorrhage in the germinal matrix, II is IVH without ventricular dilatation, III is IVH with ventricular dilatation and IV is IVH with parenchymal haemorrhage [42]. A tenth (10%) of the 497 infants who survived in the EXPRESS study developed an IVH grade III or IV, which is considered to be severe [20]. Low-grade IVH (grade I-II) has been found in 20-35% of children born preterm [43,44]. The mortality for IVH grade I have been found to be 4 %, grade II 10 %, grade III 18 % and grade IV 40 % respectively [45].

2.4.2 PVL

PVL can be divided into cystic PVL and non-cystic diffuse PVL. Cystic PVL consists of focal necrosis with cell loss [46] and this affected 6% of the children in the EXPRESS study [20]. Now non-cystic diffuse white matter injury is the most common brain injury in children born preterm. It has been found to affect more than 50% of children born EPT at term age [9,46].

2.4.3 Diffuse white matter injuries

The pathogenesis of a diffuse white matter injury (Figure 2) includes inflammation and ischaemia pathways with microglia activation, excitotoxicity and free radical attacks that give rise to pre-oligodendocyte injuries [47].

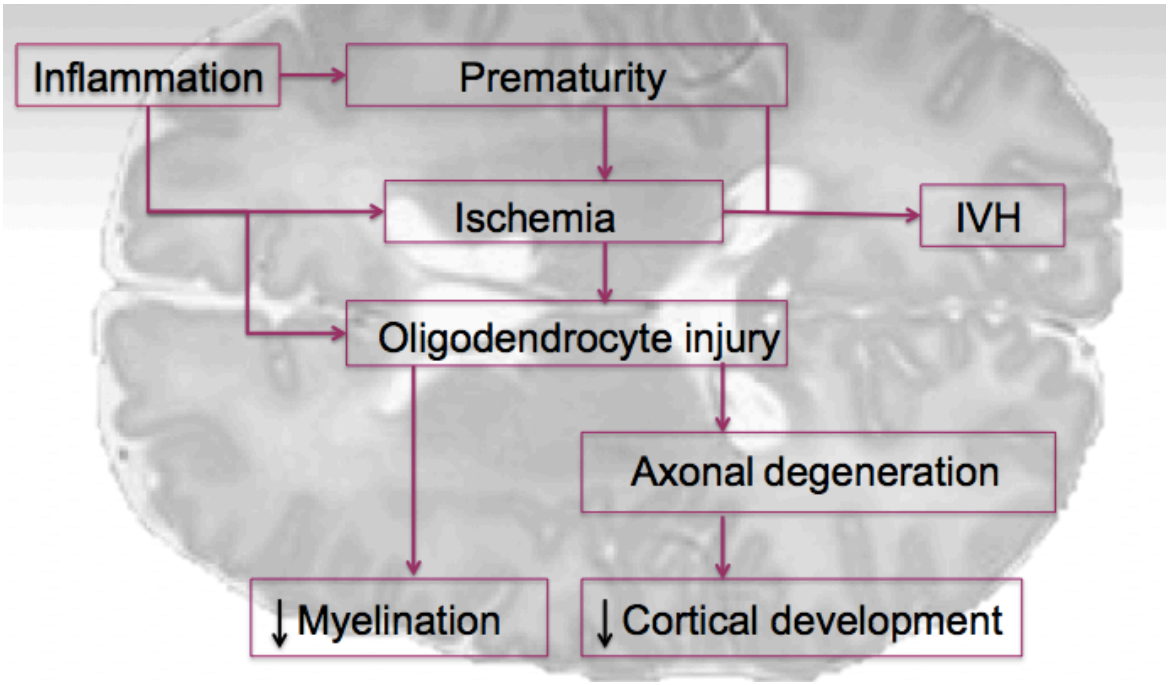


Figure 2. Proposed pathogenesis of diffuse PVL [9]

Our research group recently described white matter abnormalities (WMA) on the brain MRIs of 68 children born EPT at ten years. This showed that 37% had no WMA, 52% had discrete ones ('squared' margins of the lateral wall of the ventricles), 2% had periventricular signal changes, and 2% had cysts and extensive changes. None of the children had periventricular signal changes plus volume loss [48].

2.4.4 Grey matter injuries

The development of grey matter can be disturbed by diffuse white matter injury, IVH or independently by inflammation and hypoxia. Dysmaturation, loss of function of dendrites and loss of interneurons have been described causing signal disturbance and dysmaturation of the folding of the cortex and also structures of the deep grey matter [40,49,50]. From a study in Sweden by Horsch et al [51], 11 % of 72 children born EPT had grey matter abnormality defined by a scoring protocol including the assessment of size of the subarachnoid spaces, cortical grey matter signal and cortical gyration maturation which can been seen on MRI [51].

2.4.5 Cerebellar injuries

Cerebellar injury is also often seen on MRI at term age in children born EPT and includes infarction, haemorrhage, and atrophy [52,53,37]. The underdevelopment of cerebellum (Figure 3), with loss of volume in children born EPT can be caused by different mechanisms including inset of hemosiderin, hypoxia and reduced excitatory input leading to atrophy [37].

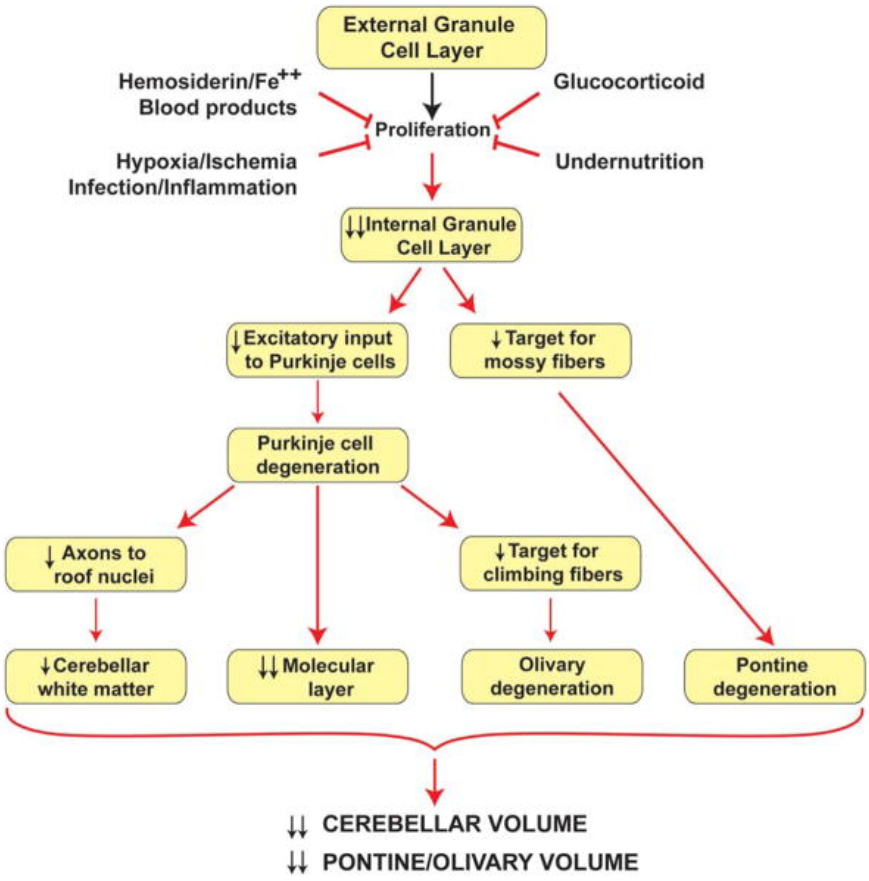


Figure 3. Proposed mechanisms causing underdevelopment of the cerebellum [37]

2.5 Neuroimaging

2.5.1 Qualitative MRI

Neonatal MRI brain scans of children born preterm are useful for identifying grey matter injuries, cerebellar injuries and diffuse WMA that are usually difficult to detect with cranial ultrasound [54-56].

The grading of the severity of WMA on MRI images at term age has been described by Inder et al [54] and been used by a number of studies of preterm cohorts [57,58,14]. WMA are commonly assessed by visual inspection of the T1-weighted and T2-weighted MRI images and are divided into four groups; no, mild, moderate or severe WMA. The criteria included thinning of the corpus callosum, the grade of myelination, reductions in the white matter volume, the presence of white matter signal abnormalities, ventricular dilatation and the presence of cysts [54]. An Australian study [59] of 86 children born very preterm at less than 30 weeks of gestation reported that 25% had no WMA on their MRIs at term age. In 63% of cases they were mild, in 7% moderate and in 5% severe WMA [59]. In another study, MRI scans was carried out when 107 children born EPT in the Stockholm region of Sweden reached term age. They

found that 14% had moderate to severe WMA and the other 86% demonstrated no or mild white matter changes [53].

Diffuse excessive high signal intensity (DEHSI) is seen as high signal intensity in the periventricular and subcortical white matter on T2-weighted images at term equivalent age in children born preterm [60]. It was first described by Maloff et al [60] and has been reported, also in subsequent studies, in 55-80% of children who were born EPT and underwent MRI scans at term age [53,60,61]. DEHSI can be an isolated finding or can be seen in conjunction with other white matter abnormalities [60]. There have been conflicting reports about whether DEHSI indicates diffuse white matter injuries or just a delay in the maturation of the white matter [61-63].

2.5.2 Brain volumes

Several authors, including our group, have reported studies showing altered brain volumes in children born very preterm and EPT [22,13]. A meta-analysis by De Kieviet et al [13] found that children born preterm had smaller brain volumes in the white matter, grey matter, and regional volumes such as cerebellum, hippocampus and corpus callosum than children born at term [13].

Thompson et al [64] reported associations between reduced brain volumes and perinatal and neonatal risk factors in preterm-born children, such as white matter injuries, intrauterine growth restriction, and BPD [64]. Keunen et al [65] also found associations between preterm birth and white matter injuries, intrauterine growth restriction, BPD, postnatal steroid treatment, and IVH [65]. Another study showed that mechanical ventilation for more than seven days, female sex and birth weight were negatively associated with global brain volumes in children born EPT who underwent MRI scans at 30 weeks of gestation and at term age [5].

2.5.3 Developmental outcomes after preterm birth

The risk of an adverse neurodevelopment after preterm birth increases with decreasing gestational age [66-68]. The incidence is also affected by age at assessment. Although the prevalence of cerebral palsy (CP) has decreased in the last decades, with a prevalence of 6.8% children born preterm in a recent review, other neurodevelopmental impairments are commonly present in children born preterm [69].

A study from the United States included 2566 EPT born toddlers assessed at 2 years with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [4]. Severe NDI was defined as motor or cognitive score below 70, CP as Gross Motor Function Classification System (GMFCS) level > III, bilateral hearing or blindness. Motor or cognitive score between 70 to 84 or CP with a GMFCS level > I was defined as moderate NDI, no/mild NDI as motor or cognitive score > 84 or no CP and CP GMFCS level I. At follow-up, 21% had severe NDI, 30% moderate NDI and 49% had no or mild NDI [4].

In a meta-analysis by Moore et al [67], 20-40% of children born between 22-24 weeks of gestation had moderate to severe NDI when they were followed up at 4-8 years of age. They

defined moderate NDI as CP GMFCS levell II-III, some useful vision, restored hearing or 2 to 3 standard deviation (SD) IQ below mean. Their definition of severe NDI was CP GMFCS level IV-V, no vision, IQ 3 SD below mean or no hearing [67].

At 8 years, Cheong et al [10] found motor impairment (below the 5th centile on MABC), in 23% to 37% of children born EPT [10]. Olsen et al [70] found motor (OR 3.9) cognitive (OR 3.7) and language (OR 5.3) impairment in children born EPT at 2 years of age compared to a term born control group [70].

Children born EPT face a higher risk of developing subtle neurological impairment than children born at term, which also affect their every day life in regard of neurological function. Minor neurological dysfunction (MND) describes a child´s neurological profile and is not a diagnosis such as developmental coordination disorder (DCD) or CP [71]. MND describes difficulties with posture, muscle tone regulation and balance, mildly abnormal reflexes, coordination and cranial nerve function [71,72]. The most common form, simple MND (MND 1) has little clinical value compared with complex MND (MND 2) associated with other developmental impairments [71,73-75]. Complex MND has been described to be associated with changes in cortico-striato-thalamo-cortical and cerebello-thalamo-cortical pathways in the brain[71]. Mikkola et al [76] studied the prevalence of MND in children born EPT and found that 17% had simple MND and 6% had complex MND [76]. In the EPIPAGE study [77], 52 % of the children born EPT had simple MND and 5% had complex MND [77].

Kurpershoek et al [78] used the Touwen Neurological Examination to examine 94 children who were born very preterm when they reached five years of age. Fifty-two percent had a normal neurology, 28.7% had simple MND and 14.9 % complex MND [78]. Children with complex MND had lower motor skills scores and a lower processing speed quotient than children with normal neurology or simple MND. However, the study did not find any differences in verbal IQ, performance IQ, working memory or visuomotor integration [78].

DCD is a diagnosis with regard to motor impairment in children born EPT, and have been reported between 9.5% and 72% in a systemic review [79]. In a recent study, DCD was reported in about 30% of the children born EPT, 13% had complex MND and 39% simple MND [80]. Peter et al [73] have discussed that there are an association between DCD and complex MND at eight years of age [73].

In relation to general cognitive outcomes, a review including children born EPT and very preterm between the ages of five to 20, the IQ was 0.86 SD below their age matched, term born peers [6]. At 19 years of age, children born EPT had significantly lower scores in IQ, visuomotor integration, visual perception, verbal and working memory and perceptual reasoning index examined with the tools Wechsler Abbreviated Scale of Intelligence, 2 ed. and Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery's VMI) compared to a control group born at term age [81]. In children born EPT, general intelligence measured by IQ scores have been shown to be 14-17 points lower than children born at term age [11].

Bolk et al [82] found the prevalence of problems in visual-motor integration to be 55% in children born EPT at 6.5 years [82]. In a meta-analysis, children at 14-20 years of age born EPT

performed 0.5 SD lower in visual motor integration test compare to their peers [11]. Executive functions in children born EPT are also affected. For example, parents to children born EPT reported higher scores of executive dysfunction compared to term born children using the assessment Behavior Rating Inventory of Executive Function at 7 years [83].

2.5.4 Brain alterations and developmental outcomes

Severe IVH (grade III-IV) and in particular focal cystic PVL, is known to be associated with severe neuromotor impairment, i.e, CP and also cognitive impairment in children born preterm [84,50]. However, the impact of low-grade IVH (grade I-II) has been debated in the literature. A review carried out by Despina et al [85], showed that it was not possible to reach a consensus about the impact of low-grade IVH on outcomes, due to the different results reported by various studies [85]. Patra et al [86] reported that children born EPT had significantly lower Bayley-III Mental Developmental Index outcomes at two years of age if they had low-grade IVH, than those without IVH [86]. However, a similar study by Payne et al [87] did not find any differences in neurodevelopmental outcomes at two years of age [87].

Only a few studies have followed up the outcomes of children born EPT with low-grade IVH at a later age. Hollebrandse et al [88] found a higher risk of CP in children born EPT with low-grade IVH when they reached eight years of age than children without IVH [88]. But they did not find differences in cognitive function or overall motor skills, using the Wechsler Intelligence Scale for Children, Third Edition (WISC-III) or Fourth Edition (WISC-IV) and the Movement Assessment Battery for Children (MABC) [88]. Campbell et al [89] did not find any associations between motor or cognitive outcomes at 10 years of age in children with any grade of IVH who were born EPT [89].

Reduced cortical grey matter volumes at term age and reduced cerebellar volume have been seen in children with low-grade IVH and associated with lower developmental quotient of motor skills at 3 years of age [90-92].

It has been reported that WMA seen on MRI brain scans at term age were predictive of neurodevelopmental outcomes in children born preterm [93]. Van't Hooft et al [94] published a meta-analysis showing that moderate/severe white matter injuries defined by Inder et al [54] described in the method section predicted CP with a sensitivity of 77% and specificity of 79 % [94].

Our group have previously reported significant differences in mean language scores and cognitive scores assessed at 30 months of age when children born EPT, with and without moderate/severe white matter injuries defined by Inder [54] were assessed with Bayley-III. However, there were no differences in the motor scores when we excluded EPT-born children with CP [14].

There have been conflicting results on the associations between DEHSI at term-equivalent age and later neurodevelopment outcomes. Some studies have suggested that DEHSI was associated with poorer developmental performance [61,63,95,96], while others did not find any associations with outcomes [97-100].

As described later in the method section, our group recently published on WMA in the brain at 10 years of age in children born EPT. However we did not find any differences in median scores in cognitive abilities with WISC-V, prevalence of MND examined with The Simplified Touwen Neurological Examination, median scores in visual motor integration with Beery's VMI-6 or median scores in motor performance with MABC-2 at 12 years of age [48].

Several studies have supporting evidence that preterm birth affects the developmental trajectory of the brain and that these alterations are associated with adverse developmental outcomes [101,65]. Reviews of children born preterm showed that their brain volumes at term age in children born preterm were associated with neurodevelopmental outcomes when they were toddlers and in childhood [101,65]. Lind et al [102] reported an association with reduced volume of cerebellum at term age and worse performance in motor skills reported by parents with Five to Fifteen questionnaire (FTF) and executive function in children born preterm at five years of age [102]. Matthews et al [103] found an association with cerebellar volumes at term age and at seven years of age in children born very preterm and scores of cognitive abilities with the Wechsler Abbreviated Scale of Intelligence, language evaluated with Core Language Index and motor performance with MABC-2 [103].

Setänen et al [104] recently published a study showing that 41 out of 98 children born very preterm had simple MND, 11 had complex MND and eight had CP. Complex MND and CP were associated with reductions in brain volumes in the basal ganglia, thalamus, cerebellum and total brain tissue [104]. The same group reported that 84% out of 98 children born very preterm had normal motor scores examined with MABC-2 at 11 years of age. They found an association between brain volumes in all regions at term age and motor scores [105].

Studying the microstructure of pathways of the motor system in the brain with diffusion MRI, Groeschel et al [106] found an association with motor performance examined with the Zürich Neuromotor Assessment at 16 years of age in children born very preterm [106].

Grey matter volume with reduction of cortical growth at term age has been associated with cognitive abilities such as memory, attention, learning and executive function [49]. Cognitive scores of Bayley-III at two years of age correlated with structural connectivity in the grey matter cortex at term age in children born prerterm [107].

Only a limited number of published studies have focused purely on children born EPT and explored the relationship between brain alterations and developmental outcomes in late childhood, which is explored in this thesis.

3 RESEARCH AIMS

The overall aim

The overall aim of this thesis was to study the relationship between brain alterations and neurodevelopment, with specific focus on neuromotor outcomes in children born EPT

The specific aims were:

- To study the differences in motor, cognitive and behaviour outcomes when children born EPT, reached 6.5 years of age, by comparing those with and without DEHSI on neonatal MRI (Paper I)

- To assess if the prevalence of MND was higher in children born EPT than term-born children at the age of 6.5 years and to study whether MND was related to other outcomes (Paper II)

- To explore the differences in motor performance and brain volumes in children born EPT, and at term, and in children born EPT with and without impairment at 12 years of age (Paper III)

- To study the impact of low-grade IVH on brain volumes and on neurodevelopmental outcomes in children born EPT when they reached 12 years of age (Paper IV)

4 MATERIALS AND METHODS

4.1 Study design and study population

This prospective cohort study followed children born EPT (before 27 weeks of gestation) from birth to 12 years of age. They were born in Sweden, between 1 January 2004 and 31 March 2007 and were partly overlapping with the EXPRESS cohort [3]

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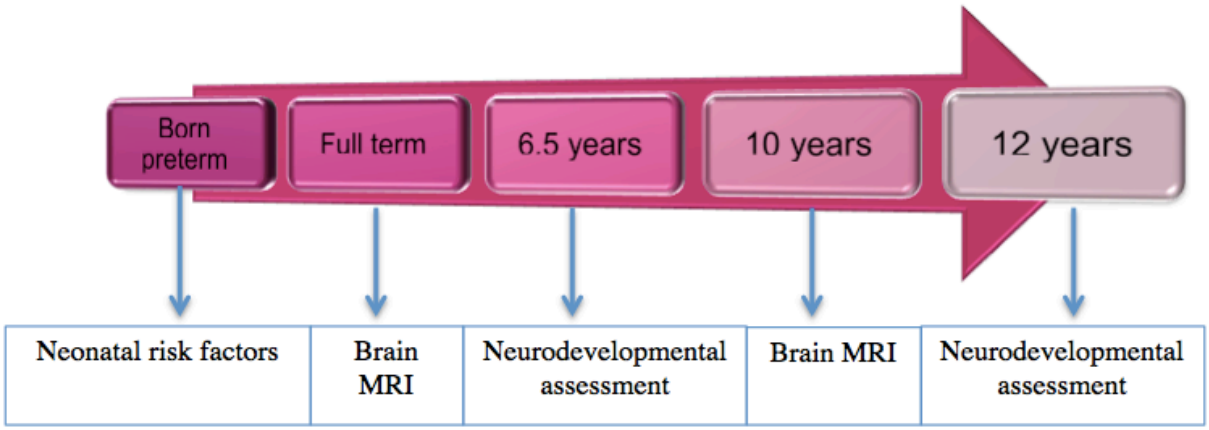


4.1.1 Children born EPT

Data on perinatal and neonatal characteristics were collected from the children´s medical records.

We examined 108 out of 129 surving children born EPT during this time period with MRI brain scans at around term age [53]. Follow-up visits with developmental assessments were performed at 6.5 and 12 years of age. At 10 years of age the children were invited to undergo an MRI brain scan.

In Study I the population comprised 108 children with MRI at term age, but we excluded 15 children with major focal lesions, moderate or severe white matter injuries and two who were over term age when the MRI scans were carried out. Of these, 66 children attended the developmental assessment at 6.5 years of age.

In Study II the population were 80 of the 118 children who were born during the specified time period and invited for a developmental assessment at 6.5 years of age. The 38 who did not take part included three children who had moved and 17 who declined to participate. We excluded nine children with CP, two with congenital cytomegalovirus infection, two with congenital malformations and one with Down syndrome. A further four children were unable to complete the neurological examination at 6.5 years of age.

In Study III, 108 children were invited for an MRI brain scan at 10 years of age and 42 scans were finally analysed.

Study IV included children born during this time period with low-grade IVH or no IVH and no major brain injury. The children underwent an MRI examination at term age and at 10 years of age and a neurodevelopmental assessment at 12 years of age. The focus was on low-grade IVH without any other major brain injury.

The study population of children born EPT in study I-IV				
Study	Invited	Excluded	Drop-out	Included
I	n=108	n=25	n=17	n=66
II	n=118	n=18	n=20	n=80
III	n=108	n=13	n=53	n=42
IV	MRI n=78 Neurodevelopmental examination n=84	MRI n=15 Neurodevelopmental examination n=2	MRI n=42 Neurodevelopmental examination WISC-V n=44 MABC-2 n=46 VMI n=70	MRI n=46 Neurodevelopmental examination WISC-V n=57 MABC-2 n=55 VMI n=31

4.1.2 Term-born controls

Term born controls were included in Studies II and III as control groups. They were recruited from the Swedish Medical Birth Registry and matched with the EPT-born subjects for postcode, age, maternal country of origin, and sex. During Study II we invited 96 term-born controls to undergo a neurodevelopmental assessment at 6.5 years of age and during Study III

77 children to have MRI brain scans at 10 years of age.

4.2 Methods

4.2.1 Overview methods in the studies

Study	Method	Method
I	Cranial ultrasound MRI at term age	Examinations at 6.5 years: Simplified Touwen, Beery's VMI-6 MABC-2, WISC-IV, SDQ
II	Cranial ultrasound	Examinations at 6.5 years: Five to Fifteen Questionnaire (FTF), Simplified Touwen, MABC-2, WISC-IV, SDQ
III	Cranial ultrasound MRI at term age MRI at 10 years	Examination at 12 years: MABC-2
IV	Cranial ultrasound MRI at term age MRI at 10 years	Examination at 12 years: MABC-2, Beery's VMI-6, WISC-V

Abbreviations: Beery's VMI-6, Beery-Buktenica Developmental Test of Visual-Motor Integration - Sixth Edition [108]; WISC-IV/V, Wechsler Intelligence Scale for Children – Fourth [109] and Fifth [110] Editions; Movement Assessment Battery for Children, Second Edition (MABC-2) [111]; SDQ, Strength and Difficulties Questionnaire [112]; Simplified Touwen, Simplified Touwen Neurological Examination [72]

4.2.2 Procedures

4.2.2.1 Cranial ultrasound

As part of the normal clinical routine neonatologists performed the brain ultrasounds during the infant's hospital stay after their birth. Ultrasound scans to detect IVH were performed during the first three days after birth and once a week until 27 weeks of age. These were performed continually once every two weeks and when the child reached term age. The descriptive data on IVH was included in every study. PVL was also assessed. Only children with low-grade IVH were included in study IV.

4.2.2.2 MRI brain scans

MRI brain scans were carried out at term age and at 10 years of age at the Astrid Lindgren's children's hospital in Stockholm, Sweden. All the MRI images were visually inspected for pathology, motion and other artifacts by a neuroradiologist and a scoring group [53]. The term MRI scans were included in Studies I, III and IV and the 10-year scans in Studies III and IV. Study III also included a control group with MRI scans at 10 years of age.

The MRI scanner used for the term-age scans was the Philips Intera 1.5 Tesla (Philips International, Amsterdam, the Netherlands) and the scanning protocol has previously been published in detail [53]. The MRI images obtained at term equivalent age were evaluated and scored for white (Figure 4) and grey matter abnormalities according to the Inder scoring system [54] as previously published [53]. Four groups were formed depending on the severity of the white matter injury: normal, mild, moderate and severe. Grey matter injuries were divided into two groups: normal or abnormal. A neuroradiologist also carried out a visual assessment of any cerebellar injuries in the MRI images [53].

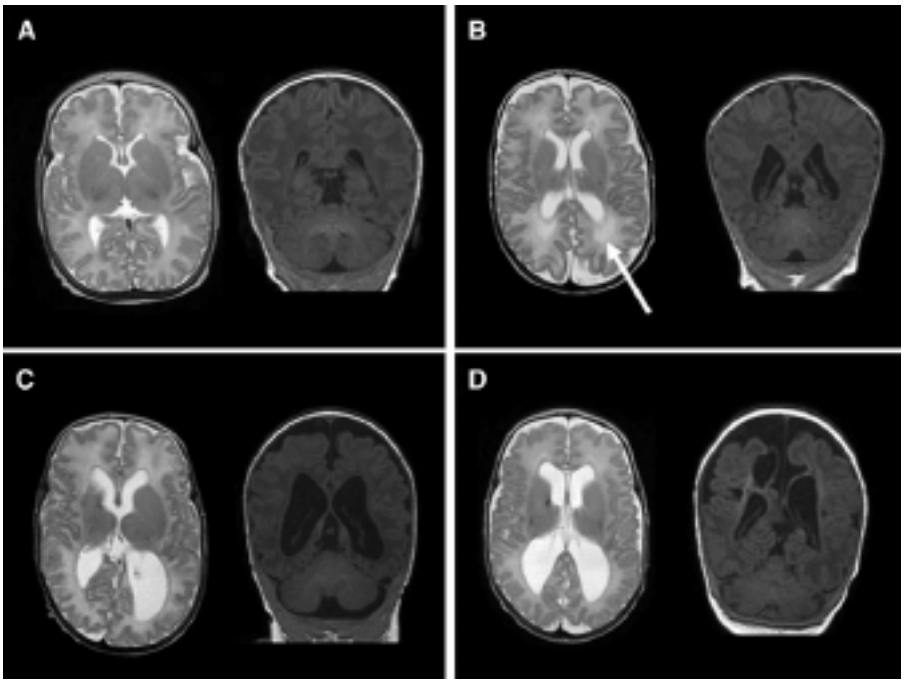


Figure 4. MRI brains scans of WMA at term age. A normal MRI scan, B mild WMA (arrow refer to DEHSI), C Moderate WMA, D severe WMA [14] Reprinted from The Journal of pediatrics 2012; 160: 559-66. Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. Copyright (2022), with permission from Elsevier

At term age, the T2 weighted images were evaluated to detect DEHSI (Figure 5). The assessments were carried out by a paediatric neuroradiologist and trained paediatrician, with good inter-rater agreement (91%, kappa = 0.807, $p < 0.005$). The evaluations indicated whether DEHSI was present and, if it was whether it was frontal, occipital, unilateral or bilateral.

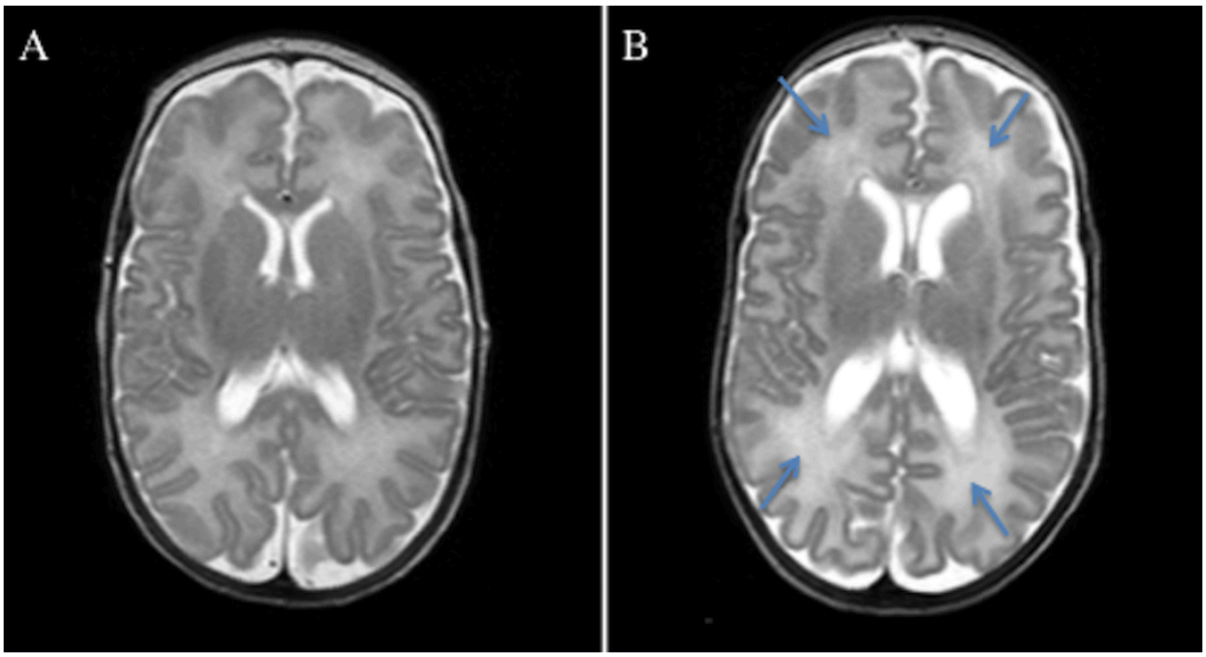


Figure 5. Axial T2-weighted MR images. Normal white and grey matter (A) and diffuse excessive high signal intensity (DEHSI) in the frontal and occipital white matter bilaterally (B). Blue arrows indicate the presence of DEHSI [113]

At 10 years of age the MRI scans were performed using a Sigma 3.0-T MR scanner (GE Healthcare). The MRI protocol included a sagittal 3D-T1 and T2 weighted with a BRAVO SPGR sequence: time to inversion = 400 ms, field of vision = 240 × 240 mm^2; f lip angle = 12°; voxel size 1 × 0.938 × 0.938 mm^3 and slice thickness = 1.0 mm.

Discrete WMA were assessed at 10 years of age and scored into four groups of severity and visually assessed by two neuroradiologists: IV with extensive change and cysts, III periventricular signal changes and volume loss, II periventricular signal changes and I that is 'squared' margins of the lateral wall of the ventricles. Details have previously been described [48].

4.2.2.3 Brain Volumetry

We assessed the volumes of 90 brain regions from the MRI scan at 10 years of age. First the T1 weighted three-dimension (3D) images were pre-processed to remove non-brain tissue and re-orientate and neck crop them [114]. Then, 90 anatomical brain regions were extracted according to an automated anatomic labeling atlas-AAL [115]. The AAL was registered to the T1 image of each child, using the Linear Image Registration Tool FSL FLIRT (FMRIB, John Radcliffe Hospital, Oxford, UK). Then, the generated deformation field was used to transform the label atlas from atlas space to subject. To calculate the atlas volumes of the regions in the brain, we used a script written in MATLAB (MathWorks, Massachusetts, USA). We chose to define volumes of structures involved in the brains motor network (Figure 6-8) and regions in Paper III [116-119].

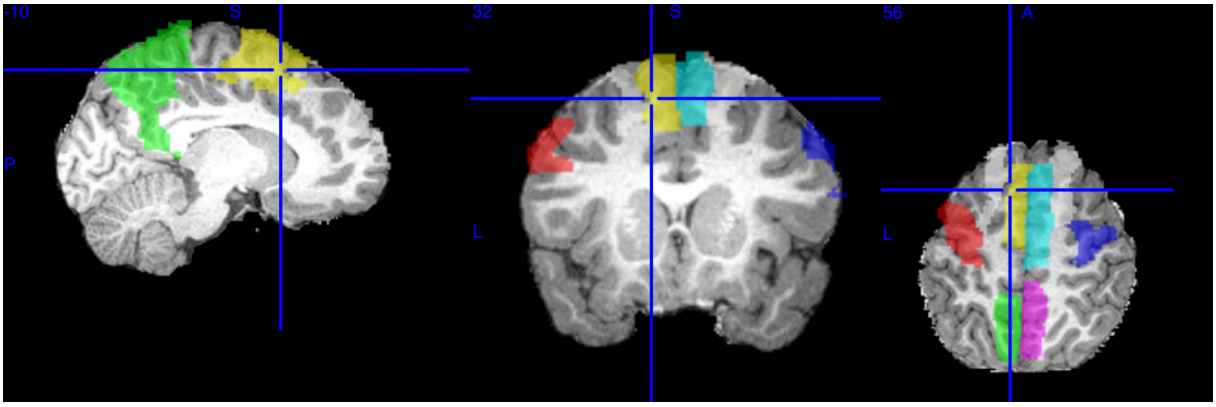


Figure 6. Volumes of the motor imagery network: precuneus (green and purple), supplementary motor area (grey), superior frontal gyrus (yellow and light blue), precentral gyrus (red and dark blue)

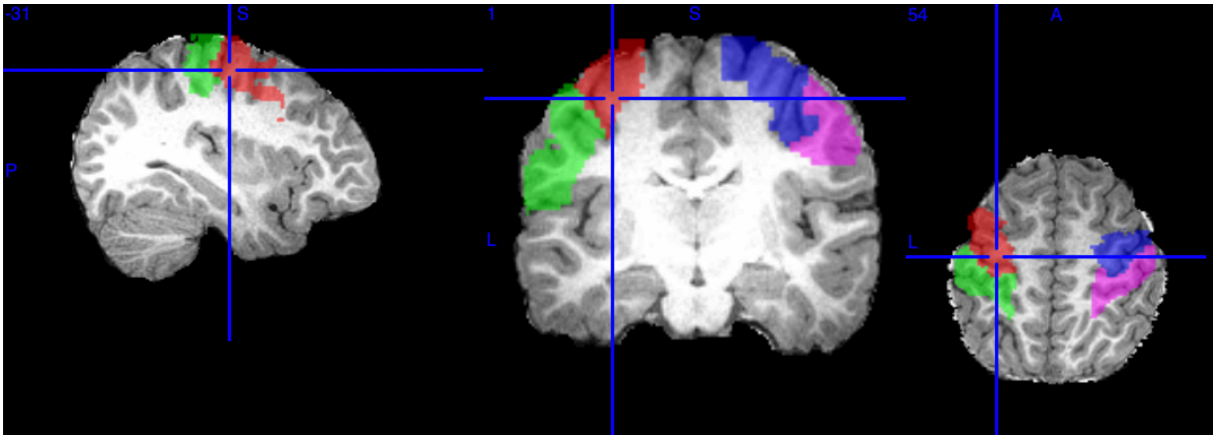


Figure 7. Volumes of the motor execution network: precentral gyrus (red and blue) and postcentral gyrus (green and purple)

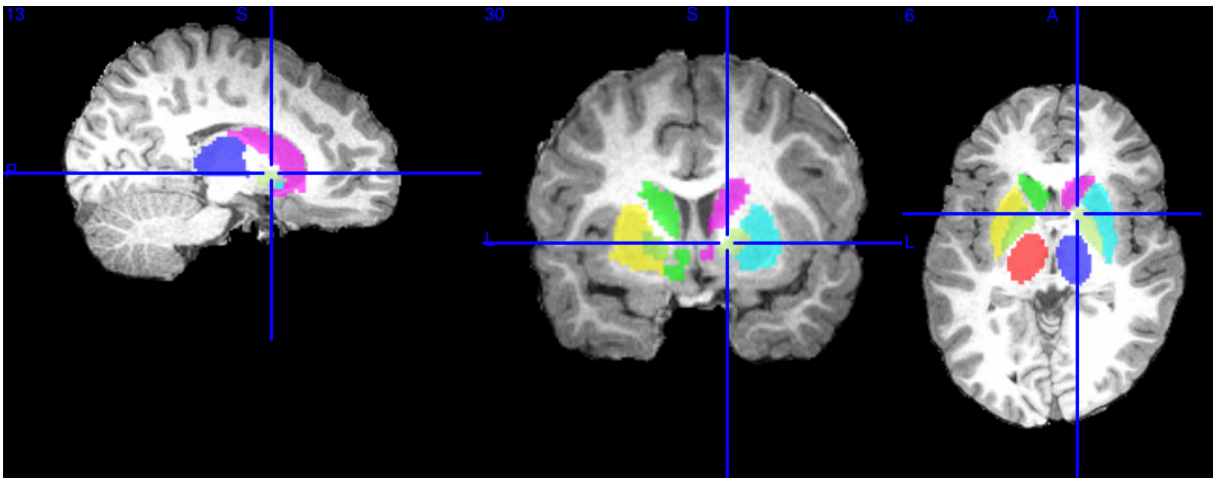


Figure 8. Volumes of the basal ganglia (yellow, green light blue and purple) and thalamus (red and dark blue)

We used two approaches to extract the cerebellar volumes. For Paper III we manually segmented each 3D MRI image of the cerebellum (Figure 9) with ITK-SNAP software [120]. For Paper IV we used FreeSurfer software, version 7.2.0 (https://surfer.nmr.mgh.harvard.edu) [121], which automatically segmented the cerebellar volume (Figure 10) from the 3D T1-weighted MRI images in white and grey matter volume (Paper IV).

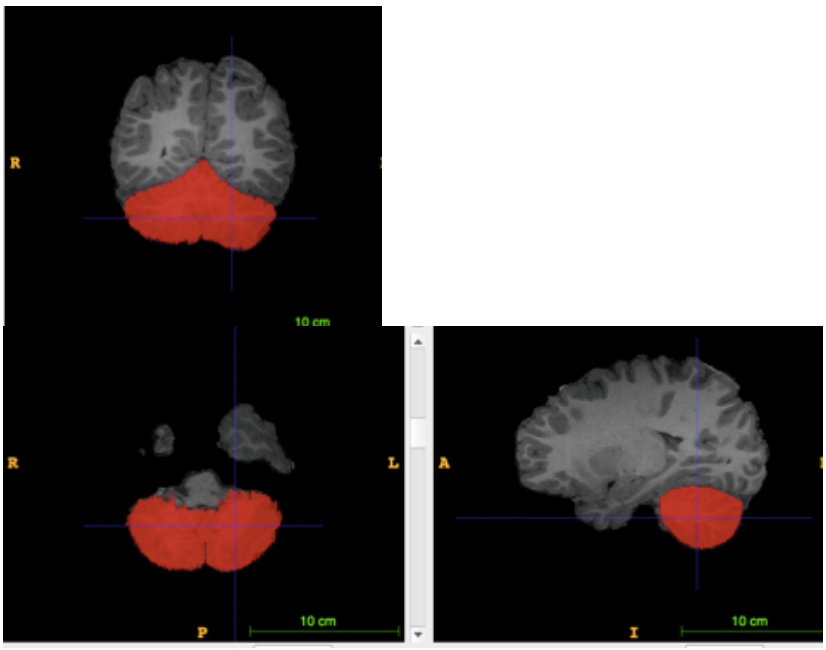


Figure 9. Manually segmented cerebellar volume (Paper III)

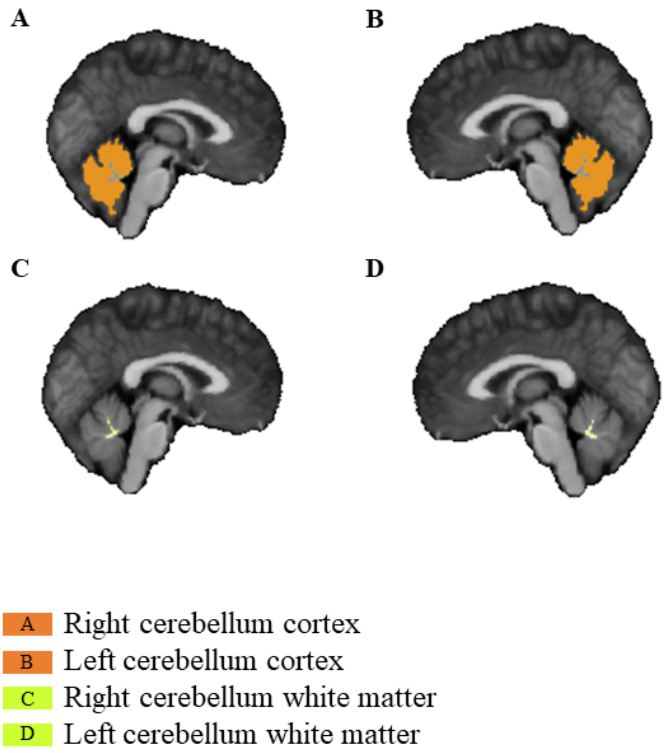


Figure 10. Automatic segmentation of cerebellar volume with Freesurfer (Paper IV)

4.2.3 Neurodevelopmental assessment

The children were invited for neurodevelopmental assessments using the following assessments at 6.5 years and 12 years of age.

4.2.3.1 Simplified Touwen Neurological Examination

The Simplified Touwen Neurological Examination[72] was performed at 6.5 years of age to examine the children's neurological profiles, MND. It evaluates more subtle neurological problems than CP and at this age MND are assessed based on four domains: posture and muscle tone, reflexes, coordinationand balance, nerve function of the face and eyes. The definition of normal, simple and complex MND is age specific and we used the classification at 6 years based on the Touwen manual [122]. Simple MND is assigned if one or two domains deviate from normal. If there is more than 2 deviant domains complex MND is assigned [72,71,123].

Simplified Touwen Neurological Examination	
Domain	Test
<u>1. Muscle tone</u> **Posture** Sitting	Deviant posture

Standing Walking **Passive muscle tone in** Elbows Ankles **Active muscle tone in** Elbows Hand Ankles	 No resistance/great resistance No resistance/can overcome a great resistance
<u>2. Reflexes</u> Biceps Patella Achilles	None/clonus
<u>3. Coordination and balance</u> Finger to nose test Diadochokinesis Romberg Standing on one leg Walking along a straight line	 Touches nose each time with a smooth movement/misses every time and tremors No pronation/supination/Soft and even pro/sup and only <5cm movement of the elbow No balance/excellent balance without movement in the rest of the body Can't stand on one leg/can stand for >20 seconds Can't take 2-3 steps along the line/no deviations on the line
<u>4. Other</u> Abnormal facial or eye movement	Asymmetry in test of the facial nerve or deviation in position of the eyes

Simplified Touwen Neurological Examination with examination of balance and reflexes

4.2.3.2 Movement Assessment Battery for Children, Second Edition

The children were examined with MABC-2 at 6.5 and 12 years of age. The test describes the child's fine and gross motor skills and includes three domains: ball skills, manual dexterity, and balance. Age-specific standard scores and centiles are calculated from the test scores. Definite motor impairment is defined as ≤5th centile and borderline motor impairment as ≤15th centile. Centiles above 15 indicate no motor impairment [111].

The MABC-2 examination, showing the tests included in each domain

Domains	**At 6.5 years of age**	**At 12 years of age**
Manual dexterity	Posting coins with hand	Turning pegs
	Threading beads	Putting bolts on a triangle
	Drawing trails	Drawing trails
Aiming and catching	Catching a beanbag	Catching with one hand
	Throwing a beanbag onto a mat	Throwing item at a wall target
Balance	Balancing on one leg	Balancing on two boards
	Walking with heels	Walking backwards toe to heel

	raised	
	Jumping on mats	Hopping in a zig-zag motion

MABC-2 examination at 6.5 years of ball skills, manual dexterity

MABC-2 examination at 12 years of manual dexterity, balance and ball skills

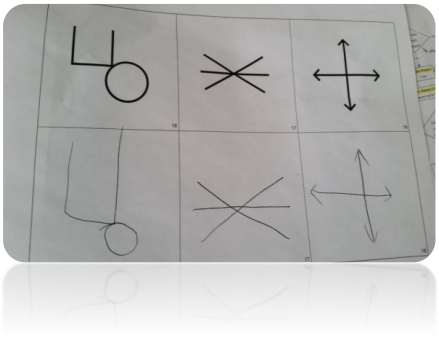
4.2.3.3 Wechsler Intelligence Scale for Children – Fourth and Fifth

Cognitive abilities were assessed at 6.5 years of age with the WISC-IV and at 12 years of age with WISC-V. The following subtests (composite scores) were included at 6.5 years of age: verbal comprehension, working memory, processing speed of information and perceptual reasoning [109]. At 12 years of age, the included subtest (index scores) were: processing speed, working memory, verbal comprehension, visual spatial, and fluid reasoning index [110].

4.2.3.4 Beery-Buktenica Developmental Test of Visual-Motor Integration-Sixth Edition

Visual motor integration (VMI) was assessed at 6.5 and 12 years of age. It examines the child's ability to integrate visual and motor skills. The child used paper and pen and copied

geometric shapes that went from easier to more complex. Raw scores are transformed into age-adjusted standard scores, where cut-offs for clinically problems are 70 and the mean is 100 with a standard deviation of 15 [108].



VMI examination at 6.5 years of age

4.2.3.5 Strength and Difficulties Questionnaire

The SDQ is a questionnaire that was completed by the child's parents and teachers to evaluate their behaviour in Paper I and II. It comprises four scales: peer relationship problems, hyperactivity/attention, and emotional symptoms and conduct problems. The scores in the parent version were divided into: normal (0-13), borderline (14-16) and abnormal (17-40) and they were normal (0-11), borderline (12-16) and abnormal (16-40) in the teacher version [112].

4.2.3.6 Five to Fifteen questionnaire

The FTF questionnaire is completed by the child's parent and consists of 181 questions about social skills, executive function, motor performance, memory, language, behaviour and learning [124]. It is a helpful tool to assess how the parents find their child´s everyday function in life.

The parent answered the questions while the child underwent the 6.5-year examination. In Paper II, information about the fine and gross motor skills was used. The scores for the questions were transformed to an age specific centile and scores above the 90th centile indicate problems.

4.2.4 Statistical analysis

SPSS version 22 (IBM Corp, New York, USA) was used for the statistical analyses in Papers I and II and version 26 was used for Papers III and IV. In general, a two-sided *p* value of less than 0.05 indicated statistical significance.

We used the chi-square test for trends, Kendall's tau-b, the chi-square test or Fisher's exact test to compare the categorical data between the groups. The student's *t*-test, Mann–Whitney U test, analysis of variance or Kruskal-Wallis test was used for continuous data, as appropriate. Analysis of covariance was used to analyse data when we included covariates to compare continuous outcomes. Logistic regression was used for categorical data and multiple linear regressions were used for independent variables. Cohen's kappa was used for inter-

rater variability in Paper I. The Benjamini-Hochberg procedure was used for the data in Paper III, to control for the false discovery rate with multiple comparisons.

4.2.5 Ethical considerations

The regional ethics committees in Lund and Stockholm provided ethical approval and written, informed consent was obtained from the parents of all study participants.

The MRI scan did not cause any pain at either age and were stopped if the child did not want to proceed. The neurodevelopmental assessment was playful and did not involve any painful procedures. An experienced neuroradiologist carefully examined the findings of the MRI brain scans for incidental findings in both the preterm and term-born groups and follow-ups were arranged, as appropriate. Referral and follow-up visits were also arranged if the children displayed any problems during the neurodevelopmental assessments at 6.5 and 12 years of age.

5 RESULTS

5.1 Paper I

We found that 59% of the 66 included in the study showed DEHSI on their neonatal MRI. This was bilateral in 95% of cases and 59% had both occipital and frontal DEHSI. There were no significant differences in neonatal morbidities between the children with and without DEHSI.

We did not find any differences in outcomes at 6.5 years between the groups, even when we adjusted for birth weight. There were no significant differences in outcomes in children with DEHSI in different regions of the brain compared with EPT born children without DEHSI

Excluding children who displayed grey matter abnormalities and cerebellar injuries on their MRI scans at term age did not change the results.

	DEHSI (n = 39)	No DEHSI (n = 27)	p-value
Age at assessment (months), uncorrected, median (range)	77.22 (75.29–82.18)	77.20 (76.03–86.33)	0.40
Neurology	n = 37	n = 27	
Normal, n (%)	19 (51)	11 (41)	
MND 1, n (%)	15 (41)	12 (44)	
MND 2, n (%)	2 (5)	1 (4)	
CP-diagnosis, n (%)	1 (3)	3 (11)	
Normal/MND 1, n	19/15	11/12	0.60[a]
Normal/MND 2+CP, n	19/3	11/4	0.41[b]
Motor function	n = 37	n = 26	
Total test score, mean ± SD	68 ± 15	66 ± 19	0.60
Manual dexterity, median (range)	23 (8–35)	26 (7–38)	0.92
Aiming and catching, mean ± SD	17 ± 5	18 ± 5	0.48
Balance, median (range)	29 (7–36)	28 (12–36)	0.28
Cognition	n = 38	n = 26	
Total scaled score, mean ± SD	87 ± 20	82 ± 18	0.33
Speed, mean ± SD	16 ± 5	15 ± 4	0.53
Perceptual, mean ± SD	27 ± 7	26 ± 7	0.59
Working memory, mean ± SD	14 ± 4	13 ± 3	0.39
Verbal, mean ± SD	29 ± 8	27 ± 8	0.27
Visual Motor Integration (VMI)	n = 37	n = 27	
Standard score, mean ± SD	92 ± 14	88 ± 11	0.23
Strengths and Difficulties (SDQ)	n = 39	n = 26	
Overall raw score, median (range)	7 (0–27)	10 (0–26)	0.59
Emotional problems, median (range)	1 (0–9)	2 (0–8)	0.49
Conduct problems, median (range)	1 (0–7)	1 (0–7)	0.41
Hyperactivity, median (range)	3 (0–10)	3 (0–9)	0.90
Peer problems, median (range)	1 (0–6)	1 (0–5)	0.70
Prosocial, median (range)	9 (4–10)	9 (4–10)	0.98

Significant value, $p<0.05$, SD = Standard Deviation, MND = Minor Neurological Dysfunction, CP = Cerebral Palsy.

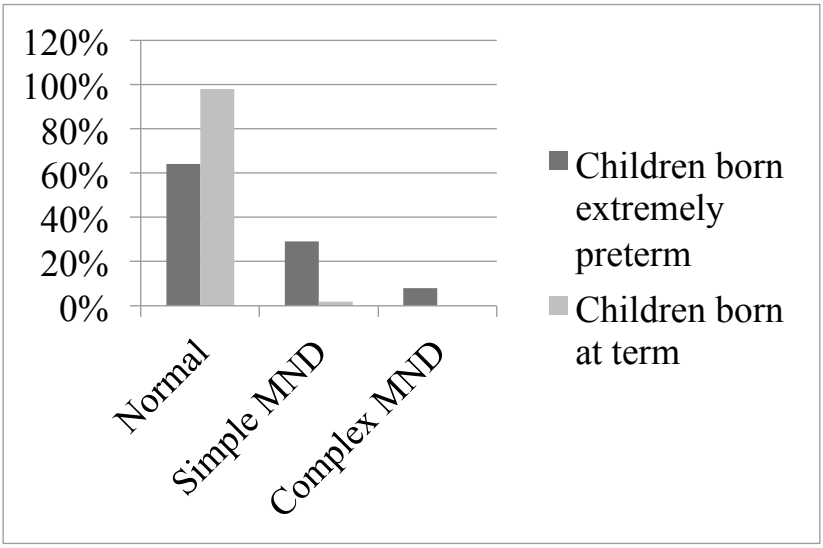
[a] Comparing normal neurology and MND 1 and

[b] Comparing normal neurology and MND 2+CP.

Outcomes at 6.5 years in children with and without DEHSI[113].

5.2 Paper II

The prevalence of MND in children born EPT was higher than the control group of term-born children at 6.5 years of age. 23 children born EPT had simple MND, six complex MND and 51 normal neurology, two had simple MND and the rest normal neurology in the control group. The degree and prevalence of MND was associated with male sex.



The percentage in prevalence of MND at 6.5 years in the study group

The number of children with dysfunctional domains in The Simplified Touwen Neurological Examination		
Dysfunctional domain	Simple MND	Complex MND
Posture and muscle tone	n=7	n=6
Reflexes	n=5	n=2
Coordination and balance	n=14	n=6
Nerve function eyes and face		n=5

Table II: Motor, cognitive, and behavioural assessment within the preterm group

Examination	Normal neurology	MND 1	MND 2	*p*
MABC-2	*n*=49	*n*=22	*n*=6	
Median total test score (range)	74 (47–97)	50 (27–91)	51 (27–56)	<0.001[a]
Manual dexterity, component score, median (range)	26 (5–38)	20 (7–34)	15 (3–23)	<0.001[a]
Median aiming and catching, component score (range)	18 (9–27)	14 (7–27)	13 (6–19)	0.002[a]
Median balance, component score (range)	30 (14–36)	21 (7–36)	20 (9–28)	<0.001[a]
FTF parents				
Gross motor problems, *n* (%)	11/43 (26)	8/18 (44)	3/3 (100)	0.009[a]
Fine motor problems, *n* (%)	9/41 (22)	7/17 (41)	2/4 (50)	0.090
WISC-IV	*n*=49	*n*=20	*n*=5	
Median FSIQ (range)	89 (71–120)	85 (66–108)	76 (57–81)	0.005[a]
Median processing speed (range)	91 (70–128)	80 (56–109)	75 (68–88)	0.033[a]
Median perceptual reasoning (range)	94 (71–125)	90 (67–110)	84 (71–88)	0.035[a]
Median working memory (range)	83 (59–116)	80 (52–97)	65 (54–83)	0.047[a]
Median verbal comprehension (range)	99 (69–138)	93 (69–126)	89 (65–96)	0.020[a]
SDQ parents	*n*=50	*n*=23	*n*=5	
Median overall raw score (range)	7 (0–28)	7 (2–26)	13 (10–18)	0.021[a]
Median emotional problems(range)	1 (0–9)	2 (0–9)	3 (0–5)	0.392
Median conduct problems (range)	1 (0–7)	2 (0–7)	1 (1–2)	0.067
Median hyperactivity (range)	2 (0–9)	3 (0–9)	4 (3–8)	0.107
Median peer problems (range)	1 (0–6)	0 (0–6)	4 (4–6)	0.003[a]
Median prosocial (range)	9 (4–10)	8 (5–10)	8 (6–10)	0.359
SDQ teacher	*n*=32	*n*=15	*n*=3	
Median overall raw score (range)	4 (0–20)	9 (0–21)	–	0.036[a]
Median emotional problems (range)	0 (0–9)	1 (0–7)	–	0.242
Median conduct problems (range)	0 (0–5)	1 (0–4)	–	0.204
Median hyperactivity (range)	0 (0–10)	4 (0–9)	–	0.019[a]
Median peer problems (range)	0 (0–4)	1 (0–5)	–	0.192
Median prosocial (range)	9 (3–10)	7 (1–10)	–	0.164

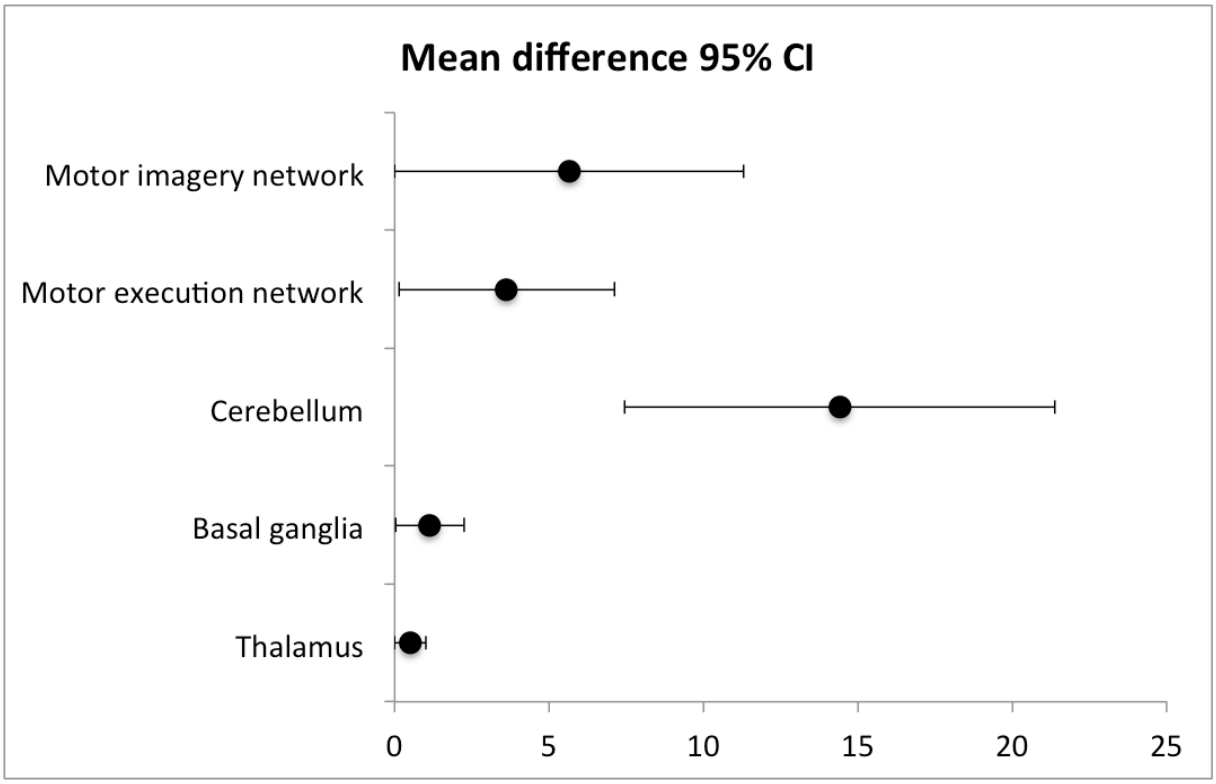
[a]Significant *p* value. MND, minor neurological dysfunction; MABC-2, Movement Assessment Battery for Children, Second Edition; FTF, Five to Fifteen questionnaire; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; FSIQ, Full-scale IQ; SDQ, Strengths and Difficulties Questionnaire.

The results of the MND findings and their associations with other developmental outcomes [125]

Children born EPT with either complex or simple MND had significantly lower motor scores compared to the children with normal neurology. MND was a predictor of motor skills adjusting for confounders. Parent reported problems in gross motor skills were associated with MND. Regarding cognition, children with normal neurology had higher cognitive score compared to the children with complex MND. MND was a predictor of cognitive abilities when adjusting for sex, gestational age at birth and postnatal steroid treatment. Peer problems and overall behaviour problems reported by their parents were more common in the children born EPT with complex MND then children with normal neurology.

5.3 Paper III

Overall motor skills, balance and coordination, ball skills and dexterity, all total scores on the MABC-2 were lower in children born EPT than in term-term controls at 12 years of age. Volumes of the basal ganglia, thalamus, cerebellum, motor execution network and the motor imagery network were significantly reduced in the children born EPT compared to term-born children at 10 years of age. This was still the case when we adjusted for intracranial volume and multiple comparisons. Children born EPT with definite ball skills problems (≤ 5 centile) had reduced volumes in the following predefined regions and networks: basal ganglia, cerebellum, motor execution network and the motor imagery network, than children without definite motor impairment.



Comparisons of mean volume differences in cm^3 in regions related to motor networks between children born EPT who did, and did not, display motor impairment in the ball skills test

5.4 Paper IV

Out of the 46 children born EPT with high quality scans, fifteen children had low-grade IVH and 31 did not. There were significant differences between the groups with regards to gestational age at birth, more days on mechanical ventilation, a higher incidence of NEC and higher levels of surgical ligation for PDA. We did not find any differences in cerebellar volumes, left and right cerebellar hemisphere, white and grey matter, motor skills, cognitive abilities or VMI between the children with and without low-grade IVH.

6 DISCUSSION

6.1 DEHSI in relation to outcomes

It has been debated whether MRI scans that show DEHSI in white matter indicate an impact on future development. In our material of EPT born infants and children, we did not find any differences in outcomes at 6.5 years with DEHSI compared with those without DEHSI.

DEHSI is a common finding in the preterm population and it was found on 59% of the neonatal MRI scans in our study. Other studies have reported rates from 74-93% [126] [127]. Morel et al [127] did not find any association between DEHSI and the neurodevelopmental scores (ages and stages questionnaire) reported by parents when their preterm-born children reached two years of age [127]. These findings were in line with our results. A meta-analysis by Rath et al [139] concluded that DEHSI was not associated with cognitive abilities or CP. On the other hand, Dyet at al [61] studied preterm-born children with DEHSI when they reached 18 months and found that they had worse Developmental Quotients on the Griffiths Scales (hearing and speech, personal-social, motor, practical reasoning eye/hand coordination) than children born preterm without DEHSI [61]. Also, Mürner-Lavanchy et al [126] found that DEHSI was associated with adverse development in EPT born children at 13 years of age, including association of impaired planning abilities, but not behaviour, motor skills or other cognitive abilities [126].

It is not fully understood what DEHSI represents from a histological point of view and whether it is an underlying pathology or not. Volpe [128] described DEHSI as white matter gliosis with a white matter injury [128]. However, histological findings have showed that DEHSI consists of remnants of the subplate at term age and later disappears and this suggests that it is due to delayed maturation in white matter regions [129]. This supports the concept that DEHSI is delayed maturation.

The wide range of neurodevelopmental outcomes that were assessed is a great strength of this study. We decided to focus on isolated DEHSI without other major brain lesions that could have affected the results. Our study can confirm that DEHSI can be seen as altered white matter maturation rather than white matter injury.

6.2 The prevalence of MND and associations with other outcomes

The prevalence of simple and complex MND was higher in children born EPT than term-born children at 6.5 years and it was higher in males than females. As expected, there were also associations between MND and other neurodevelopmental outcomes.

Mikkola et al [76] found that the prevalence of MND in preterm-born children was 21% for simple MND and 7% for complex MND [76]. They also reported that males had a higher risk of MND, which was similar to our findings [76]. We found that MND was related to parental reports of cognitive abilities, motor skills, behaviour and gross motor skills. Studies have

shown associations between MND and motor skills and cognitive abilities when term-born children reached school age [75,130,74]. But there have only been a few studies of MND in children who were born preterm. MND in preterm children has been associated with learning skills reported by the parents at the five years of age[77] and motor impairment (≤15th centile) examined with MABC-2 [131].

It has been suggested that simple MND is caused by stress during early life or genetics and complex MND is associated with altered brain circuits and that cerebello-thalamo-cortical and cortico-striato-thalamo-cortical pathways are affected [71,122,123]. Complex MND in 11-year-old children who were born preterm have also been shown to be associated with reduced volumes in the cerebellum, thalamus and basal ganglia at term age [104].

The strengths of our study lie in the fact that we reported MND in children born EPT, used a control group for comparisons and included other developmental outcomes.

We expected a higher prevalence of MND in the control group than we found. The lower than anticipated rates could be a true finding or due to methodological issues, such as not using the complete Touwen examination. This could have affected the results in either direction.

6.3 Motor performance and brain regions/networks involved in motor performance

Children born EPT who were included in our study had significantly smaller brain volumes at 10 years of age than the term-born controls. In addition, children born EPT who had definite motor impairment related to ball skills at 12 years of age had significantly smaller brain volumes in their basal ganglia, motor execution network, motor imagery network and cerebellum than EPT-born children without these motor impairment.

Altered global and regional brain volumes at term age have been reported more frequently in children born preterm than at term age [65,132]. This might be due to the loss of time in the intrauterine environment and that it affects brain growth [9]. Similar to our study, Grunewaldt et al [133] have shown reduced volumes in the thalamus and cerebellum in children born with birth weights below 1000 grams, compared to term-born children, at 10 years of age [133]. Lax et al [134] found smaller volumes of basal ganglia and thalamus in children born preterm compared to term-born children when they reached eight years of age [134].

We showed that children born EPT with motor impairment in ball skills in MABC-2 at 12 years of age had reduced volumes in structures involved in the brains motor network at 10 years of age. This could have been due to the altered developmental trajectory in the brain and vulnerability of the brain areas involved in this function [12]. Others have also reported this. For example, Dewey et al [135] reported smaller brain volumes in children with motor impairment (≤16th percentile in MABC-2) at seven years of age in children born. The affected areas were the cerebellum, thalamus and basal ganglia [135]. Motor performance with MABC-2 total score and volumes in the cerebellum, caudate nucleus, thalamus, putamen and globus pallidus positively correlated in 10-year-old old children who were born preterm [136].

We found that the cerebellum was the most affected area of the brain in children born EPT. Several causes for the underdevelopment of the cerebellum have been discussed in the literature. For example, Volpe [37] discussed possible factors that reduced the growth of the cerebellum and could lead to disturbances in the cells in the cerebellum. These included steroids, undernutrition, inflammation and hypoxia [37].

Our study has shown new important findings that describe the association with brain volumes in structures involved in the brains motor network and motor outcome at late childhood in children born EPT. The children with definite problems in ball skills have smaller volumes of region and motor networks in the brain. As ball skills are likely to be related to training [137], a limitation of the present work is that we did not collect information about ball game activity level of the children.

6.4 Low-grade IVH and the impact on cerebellar volume and outcomes

In our current data, low-grade IVH was not related to any differences in cerebral or cerebellar volumes at 10 years of age or in neurodevelopmental outcomes at 12 years of age in children born EPT.

Previous studies have yielded conflicting results. Some studies have found associations between low-grade IVH and outcomes at two years and at school age [88,86], but others have not [87,89]. However some of the studies did not make it clear whether they excluded children with major brain injuries. When we excluded major injuries, we did not find any differences in cognitive abilities, motor performance or VMI between children born EPT with and without low-grade IVH.

Our study was able to focus on low-grade IVH without major brain lesions. We had detailed information on ultrasounds and MRI brain scans and follow-up data. Other factors could have influenced the results of the neurodevelopment assessments at 12 years of age, such as motor training and environment.

An overall limitation in the studies of this thesis is the sample size of the cohort included. The small sample size contributes to a limitation in interpretation of the results. Many of the morbidities that affect these children influence both brain development and neurodevelopmental outcomes, however with a limited sample size too many statistical adjustments are not possible. During all neurodevelopmental assessments, the examiners were supposed to be blinded to the gestational age of the child. However, often the examiner could tell if the child was born EPT or not by clinical experience. At both 6.5 and 12 years of age, the participating children were examined during a whole day including cognitive-, VMI-, motor- and neurological assessments. This required the children to stay focused for a very long time, which is not an easy task for any child.

7 CONCLUSIONS

- DEHSI on MRI at term age was not associated with developmental outcomes in children born EPT at 6.5 years of age

- At the age of 6.5 years, MND both simple and complex, were more common in children born EPT than in term-born children

- Children born EPT with simple MND and complex MND had more impairments in motor skills, everyday motor skills, general cognitive abilities, and behaviour than those with normal neurology at 6.5 years of age

- EPT birth had a long-term influence on motor development at 12 years of age and on the brain volumes involved in motor function at 10 years of age

- Ten year old children born EPT with impaired ball skills had reduced volumes in the basal ganglia, cerebellum and motor networks in the brain compared to EPT born children without ball skills impairment

- Children born EPT with low-grade IVH did not have smaller cerebral or cerebellar volumes at 10 years of age or worse neurodevelopmental outcomes at 12 years of age than children born EPT without low-grade IVH

8 POINTS OF PERSPECTIVE

Neuroimaging has developed in the last 20 years and it provides detailed information in children born preterm. Cranial ultrasound is the standard bedside examination in the neonatal intensive care and, in some centers, additional routine MRI brain scans are carried out at term age [52]. There have been discussions about whether MRI brain scans should form part of the routine clinical examination for children born preterm. MRI scans at term age have been shown to be a better tool for identifying non-cystic white matter injuries and cerebellar injuries and for predicting neurodevelopmental outcomes. They also have a good negative predictive value for neurological impairment later in life [52], meaning it could be reassuring for the parents if the MRI scan is normal at term. Edwards et al [138] showed that there was reduced maternal anxiety in mothers of preterm born after MRI brain scan at term age, whereas an ultrasound examination did not confer the same relief [138].

DEHSI was only seen on the MRI scans of preterm-born children when they reached term age [139] and this raises the question about whether these findings were pathological or not. We found that DEHSI did not have impact on a whole range of neurodevelopmental outcomes at 6 years of age. Our conclusion was strengthened by a recent review [139]. The results are reassuring when you consider how frequently DEHSI appears on the MRI scans of preterm children.

Our study shows the importance of identifying children with more subtle neurological problems than CP. Therefore it is important to pay attention to subtle neurological signs in follow-up studies of preterm-born children. Parents have reported that MND affects children's motor performance in their daily life. Our study underlines the importance of follow-up studies, with multidisciplinary input, after children are born EPT. The problems that have an impact on their everyday lives include playing with peers and struggling with motor impairment.

In general it is of importance to study how the most immature babies develop later in life due to the problems they are facing with neurodevelopmental impairments. The children in this study were followed since birth and received neurodevelopmental follow-up assessments at 6.5 and 12 years of age, together with a control group. It is of great importance to show development over time and the more evidence based research we can provide the more information we have to society and health care to help the children that have problems.

Early interventions including parental support have been shown to transiently improve cognitive and motor outcomes in children born very preterm [140,141]. However, it is still unclear whether the intervention is effective in EPT born children in the Swedish context. In contrast to other countries we have long parental leave and high support through child health care services, which could influence the outcomes. There is an important on-going randomized clinical trial called the Stockholm Preterm Interaction-Based Intervention[142], which provides home visits during the first year of life to families with children born EPT in order to improve their outcomes. If the intervention proves effective, it is important that this project is established in clinical practice.

We found reduced volumes in the motor networks of children born EPT when they were compared to term-born children at 10 years of age. Thus the early effects on brain growth are not corrected during childhood, but EPT born children continue to have smaller brain volumes. Brain volume measurements are still carried out on a research level, but maybe in the future they could be used to predict outcomes in clinical settings.

Children born EPT are born during a vulnerable time in their brain development and it is important to identify factors that can protect this immature organ. Kangaroo mother care and singing for infants have produced positive results, but more research is needed [143,144].

Our study has shown that low-grade IVH did not influence the cerebral or cerebellar volumes or neurodevelopmental outcomes in our cohort of children born EPT. Due to the limited size of the cohort we cannot exclude there are small differences in neurodevelopmental outcomes. The more studies that are carried out with larger cohorts and "isolated" low-grade IVH, the more confident we can be about the findings.

Children born EPT often have many morbidities, brain injuries and neurodevelopmental impairments and not just one. It is important to take their complex needs into account during childhood in preschool and school. In the future, I hope education about preterm born children´s needs for teachers and general practitioners and preventive early intervention programs for preterm children's general health could be launched.

9 ACKNOWLEDGEMENTS

Ulrika Ådén my main supervisor. Thank you for introducing me to research and welcoming me to your research group. Your knowledge and engagement in the field is really inspiring. You have made it possible for me to travel all around the world to present our research findings and meet many interesting people. You have given me the tools to become a researcher and you have showed trust in my work.

Brigitte Vollmer, co-supervisor. You are a true expert in paediatric neurology and I thank you for your knowledge and guidance during the studies in Papers I and II. Thank you for teaching me about MND and I'm very thankful for all your support and great comments when I was writing the manuscripts.

Nelly Padilla, co-supervisor. Thank you for being engaged and helpful and teaching me about MRI technology. You have made my work possible. I have really appreciated your great comments and our discussions. You have become a real friend and I will come and visit you and A!

Maria Örtqvist, co-supervisor. Thank you for your great input and knowledge about the studies in Papers III and IV. I am really grateful for your good comments and discussions!

Kristina Gemzell Danielsson, Head of the department of KBH. Thank you for being a great role model as a researcher.

Hugo Lagercrantz, neonatologist and senior professor in paediatrics. Your endless work to improve health care and always trying to make the children´s voice heard in research and society is inspiring. You are the leader of knowledge in brain development and the progress of research of the brain in the child is thanks to you.

Fredrik Stenius, head of Sachs and former clinical boss. Thank you for hiring me as a resident in paediatrics at Sachs. You have always been supportive and encouraging and knows the importance of research.

Stina Almkvist-Osterman, my clinical boss. Thank you for supporting me through life and being really been supportive of my clinical work and research. I will be back at Sachs soon!

Inger Kull, my mentor. Your advice on research has been wonderful and I am so happy to have had such an experienced enthusiastic research professor as a mentor! I hope to see more of you at Sachs.

Jenny Bolk, fellow PhD student and friend. I don't know what my life, as a PhD student would have been without you, your kindness and our great discussions about research and life. And thank you for the wonderful journeys that we have made together as PhD students!

Hedvig Kvanta, fellow PhD student and friend. I am so happy you decided to join the research group. Every hour spent segmenting brain volumes with you have been fun. And thank you for all the phone support you have provided.

Eva Eklöf, research group colleague. You were a part of the research group when I started. It was great to sit next to you at plan 7, supporting each other and getting to know you! And I will never forget our US trip, which was both fun and scary!

Lena Swartling Schlinzig, research nurse. You are fun and sharp and meeting you in the corridor always ended up with us having long chats. These studies would not have been possible without the dedication and accuracy you showed while following this cohort.

Jennifer Frithiof, coordinator and all doer. Always helpful. I will always remember the good times at plan 7, nice company, chats and lunchtime walks in the Haga Parken!

Thank you also to the members of our research group, who have all have been helpful and great to work with: **Daniela Nosko, Gustaf Mårtensson, Marika Strindberg, Carmen, Lea Forsman, Elena di Martino** and **Lexuri Fernández de Gamarra-Oca.**

Emilija Wilson, fellow phD student and desk buddy at plan 7. I miss our talks and your company!

Everyone in the **NeoBIG** and **EXPRESS** groups.

Fab-4, **Carro, Maria, Sara**! Friendship since high school and I am so grateful for having you in my life.

My lovely big family. Thank you for being in my life and I love you all.

My nieces **Elton, Miranda, Olivia** and **Elvira**. I love you as if you were my own kids. Mom and Dad, thank you for always being there no matter what. **Berit and Bert**, my grandmother and grandfather. You have always looked after me and given me love, strength and time. Berit, I wish you were here celebrating this day with us. I miss you endlessly. Bert, I couldn't ask for a better grandfather. Thank you for always teaching me things, buying me books throughout my life and always being there.

Alice, my daughter. Thank you for having long naps and sleeping in the evenings so that I could write and write. And thank you for being you. Love you.

And of course, thanks to all the **patients and parents** who took part in the studies.

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