# Chapter 1

## General Introduction

## General introduction

Preterm birth, a relatively common complication of pregnancy, occurs before 37 weeks of gestation, and comprises late preterm birth (32-37 weeks of gestation), very preterm birth (<32 weeks of gestation), and extremely preterm birth (<27 weeks of gestation) according to the World Health Organisation.[1] In general, the obstetric mechanisms leading to preterm birth are: 1) delivery for maternal or fetal indications, in which labor is either induced or the infant is delivered by caesarean section; 2) spontaneous preterm labor with intact membranes; and 3) premature rupture of the membranes, irrespective of whether delivery is vaginal or by caesarean section.[2] In 2010, an estimated 11% of all live-births worldwide were born preterm, ranging from about 5% in several European countries to 18% in some African countries, and the incidence of preterm birth is rising.[3] In this thesis, we will focus on infants that were born very preterm, which is the case for 1-2% of all live-born infants in The Netherlands.[3;4] The mortality of infants born very preterm has been considerably decreased in the last two decades as a consequence of advances in neonatal care, and by now approximately 80-90% survive the neonatal period.[5] Taken together, the total number of very preterm infants that develop into childhood and adolescence is growing, however, there is increasing awareness that developmental outcomes of this emergent group of very preterm children remain a significant problem.

Immature organs, including the brain, are extremely vulnerable for adverse effects in the neonatal period.[6;7] Development of the brain during the late second and early third trimester of gestation is normally a smoothly orchestrated series of complex and interrelated events, including neuronal migration, glial cell proliferation, axonal growth, synapse formation, myelination, programmed cell death, and stabilization of cortical connectivity.[8-10] Normally, the second half of gestation (20–42 weeks of gestational age) is a crucial period in the formation of cerebral pathways. During this period, there is an elaboration of the thalamo-cortical pathways (between 20–32 weeks of gestational age), and the development of callosal and long cortico-cortical pathways (24–35 weeks of gestational age), which format the complex circuits of the nervous system. In the third trimester of gestation (27-42 weeks of gestational age), maturation of the oligodendroglial cells and initiation of myelination occurs.[10-13] Furthermore, the volume of the cortex increases four-fold in this period.[14;15] In a healthy intrauterine environment, this maturational program is

presumed to be largely under genetic control, but can be seriously disrupted when the intrauterine or extrauterine environment in which the brain is developing is sufficiently stressed.

Multiple factors can cause alterations in brain development and perinatal brain injury, including cerebral hypoxia, ischemia, infection, and inflammation,[10] underlying lesions such as periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH). Whereas the risk for IVH appears to be most closely related to immaturity and vulnerability of tissues to hemorrhage, PVL is most likely the result of a multifactorial process associated with inflammatory, hypoxic and ischemic events, which involves cytotoxic injury and vascular compromise.[16] Furthermore, very preterm infants are at risk for perinatal infections and inflammations with associated excitotoxicity and free-radical accumulation, negatively interfering with the normal brain maturation processes.[10;17] Indeed, a broad range of studies have linked chorioamnionitis, sepsis and necrotizing enterocolitis with adverse neurodevelopmental outcomes in very preterm infants.[18] Importantly, very preterm children that have one or more of these risk factors, as well as other risk factors such as intrauterine growth restriction or a lower gestational age, may particularly be at risk for altered brain development.[19-21]

By now, it has become increasingly clear that, for the majority of very preterm infants, the negative effects on brain development are not present in the form of overt focal lesions, but are described by more subtle white and gray matter structural damage. In particular disturbance of white matter development, including the development of axons and pre-oligodendrocytes, eventually underlying differences in myelination and resultant neuronal connectivity, is prominent in very preterm children.[10] The alterations in white matter development are intertwined with cortical grey matter alterations, as cortical organization and synaptic development are facilitated by axons providing a functional link between deep brain areas and the cortex.[10;22]

**Quantification of altered brain development**

Nowadays, alterations in brain development can be reliably quantified in vivo using well-established and frequently used non-invasive techniques, including Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI). Whereas MRI can be used to determine differences in brain structure development in children, DTI is able to delineate

white matter tracts and to quantify microstructural changes not detectable on conventional MRI.[23] Using structural MRI, several studies have measured and reported reductions in brain structure volumes of very preterm children compared to term peers. Manifestations of reduced brain structure volumes at term equivalent age include both white matter volume and grey matter volume. In addition, reduced volumes of various other brain structures are reported, including the hippocampus, the cerebellum, and the thalamus,[24-28] pertaining into childhood, adolescence, and young adulthood.[29-34] Using DTI, values of fractional anisotropy (FA) can be determined based on the direction of water diffusion in the brain. The FA value is influenced by size, organization, and number of (myelinated) axons, and can be used as a measure for white matter integrity.[35] Multiple methods are available to analyze FA values as determined using DTI, including track based spatial statistics (TBSS) and probabilistic diffusion tensor tractography.[36;37] In very preterm children, significantly reduced FA values have been reported for multiple white matter pathways at various stages in development, indicating that white matter integrity remains altered in very preterm children throughout childhood and adolescence.[38-44]

**Motor, cognitive, and behavioral functioning**

As a consequence of the negative effects on brain development, long term developmental outcomes are compromised in very preterm children. Major handicaps, such as cerebral palsy (present in around 2-7%), mental retardation (4-5%), deafness (1-2%), and blindness (1-2%), are often reported.[45;46] While the rates of major handicaps occur in a minority of very preterm children, and have remained relatively constant or decreased over the last decade,[45] there is an increased awareness that the majority of very preterm children suffer from more subtle problems as they grow up.[47] A broad range of neurocognitive sequelae are found in very preterm children, of which motor and cognitive problems are predominant. Motor problems such as developmental coordination disorder (DCD), a disorder in which planning, coordination of movements, and visuomotor abilities are affected, appears to be six times more prevalent in very preterm children compared to term peers.[48] For cognition, previous studies have indicated lower intelligence quotient (IQ) scores for very preterm children, especially in very preterm children with relatively short gestation and lower birth weight.[49] Cognitive impairment of very preterm children is not limited to poorer intellectual development as indicated by lower IQ scores, other lower and higher-

order neurocognitive functions can also be affected by very premature birth. For instance, slower processing speed is frequently found in very preterm children at various ages.[50] Furthermore, recent meta-analyses by Aarnoudse-Moens et al. and Mulder et al. showed that executive functions, including inhibitory control, working memory, verbal fluency, planning, and set-shifting, were considerable poorer in very preterm children compared to term controls, with effect sizes ranging from 0.36 SD to 0.57 SD.[51-53] The subtle problems in motor and cognitive functioning of very preterm children often do not occur in isolation, and the combination of multiple adverse neurocognitive sequelae regularly interferes with adaptive functioning. Adaptive functioning refers to one's ability to effectively interact with the environment, and generally includes measures of behavioral and emotional functioning, as well as school performance.[54-56] Indeed, very preterm children have a 2.6 fold higher risk for developing attention deficit hyperactivity disorder (ADHD), and frequently manifest externalizing or internalizing behavioral problems at school age.[49;51] In the Netherlands, 38% of very preterm children born in 1983 had special assistance at school, and about 20% attended special education, compared to 4.8% of the normal population.[57] Alarmingly, the high rates of morbidity arising from very preterm birth impose an immense burden on families, education, health services, and social services.[58] Recently, the total of societal costs accompanying the high rates of morbidity were estimated at approximately 140.000 Euros for each surviving very preterm child,[59] underlining that the development of cost-effective treatments and interventions of the problems in cognitive and motor, as well as the resultant difficulties in adaptive functioning of very preterm children is of utmost importance.

**Opportunities for intervention**

It is evident that very premature birth has negative consequences, hence early developmental interventions and treatments directed at improving motor and cognitive functioning of very preterm infants as well as the resultant difficulties in adaptive functioning, such as physical therapy, occupational therapy, psychological therapy, and parent–infant relationship enhancement, have been used in the clinical setting for many years. However, a recent meta-analysis indicated that their overall effect appears to be limited, as only positive short-term improvements in cognitive development were present.[60] The question arises whether, and how, interventions can be made more successful in

effectively improving impaired functioning of very preterm children in their later lives. Importantly, reductions in brain structure volumes as well as reduced white matter integrity in very preterm children have been widely associated with the various aspects of motor, cognitive, and behavioral functioning,[29-31;33;38-40;42;43;61-70] indicating that altered brain development crucially underpins the functional problems in very preterm children. Nevertheless, the precise underlying mechanism leading from alterations in brain development towards problems in motor, cognition, and behavioral functioning, is largely unclear. Therefore, more insight into the nature of the widespread problems in motor, cognitive, and behavioral functioning, and in particular their relation with alterations in brain development, is essential in order to improve the efficacy of early interventions and treatments for very preterm children.

Some progress in the development of interventions directly aimed at reducing (the risks for) altered brain development in the neonatal period has been made.[71] Established interventions include the administration of antenatal corticosteroids to women at risk of preterm birth,[72] which may reduce the incidence of IVH and benefit brain development,[73;74] although there are some indications suggesting unfavorable outcomes for development of the hippocampus.[75] Furthermore, beneficial results have been found for moderate hypothermia on the reduction of neural damage after moderate hypoxic or ischemic events in the neonatal period.[76-77] Finally, Erythropoietin (EPO) may provide neuroprotection against neuronal apoptosis, brain edema, neurotoxicity, as well as increase neural regeneration following hypoxic or ischemic events in the neonatal period.[78] Nevertheless, development of interventions directly aimed at reducing (the risks for) altered brain development in the neonatal period of very prematurely born children is still in its infancy. Although multiple factors and complications are involved in the process underpinning altered brain development in very preterm children, one promising candidate moderator of adverse brain development is the presence of serious neonatal infections in the neonatal period. The majority of very preterm children had at least one serious infection in the neonatal period,[17] and several studies emphasize the negative effects of neonatal infections with associated excitotoxicity and free-radical accumulation on brain maturation processes and long term development in very preterm children.[17;18;79-82] Therefore, a lower incidence of serious neonatal infections may positively influence brain development, and improve long term motor, cognitive and behavioral functioning in very preterm children.

**The aims of this thesis**

The aims of this thesis are 1) to increase insight into the precise nature of the problems in motor, cognitive, and behavioral functioning of very preterm children at school age, 2) to elucidate alterations in brain development underpinning the problems in motor, cognitive, behavioral functioning of very preterm children at school age, and 3) to investigate the potential for neonatal nutritional interventions, directed at reducing the incidence of serious neonatal infections and associated alterations in brain development, in order to improve long term motor, cognitive, and behavioral functioning of very preterm children.

**Sample and study design**

To investigate these aims, a follow-up study was performed on very preterm children that originally took part in a nutritional intervention study between September 2001 and July 2003 at the VU University Medical Center Amsterdam.[83] In the original randomized controlled trial, all infants with a gestational age below 32 weeks or a birth weight below 1500 grams, who were admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam, were eligible for participation. Exclusion criteria were major congenital or chromosomal anomalies, death within 48 hours after birth, transfer to another hospital within 48 hours after birth, and admission from an extra regional hospital. Either amino acid glutamine or an isonitrogenous control supplementation (alanine) was supplemented between day three and 30 of life.[83] The potential protective effects of supplementation of glutamine in very preterm children have been extensively studied, including the modulation of inflammatory response and stimulation of immunity.[84] Experimental studies have shown that glutamine plays an important role in maintaining the functional integrity of the gut,[85;86] which in turn leads to decreased bacterial translocation and systemic spread of bacteria.[87-89] Through this cascade of events, glutamine supplementation may potentially lead to decreased infectious morbidity in the neonatal period. Promisingly, previous outcomes in the same sample as studied in this thesis, illustrated a lower incidence of serious neonatal infections in glutamine treated very preterm children compared to the placebo group.[83] Therefore, glutamine supplementation and the resultant lower incidence of serious neonatal infections, may have minimized unfavorable alterations on brain development. Taken together, these previous findings

illustrate the eligibility for using the same sample to explore the potential for nutritional interventions that aim to minimize alterations in brain development, in order to improve long term motor, cognitive and behavioral functioning in very preterm children.

The follow-up study consisted of two follow up moments. Firstly, a broad battery of motor, cognitive, and behavioral measures was assessed, which took place at the VU University Amsterdam between October 2009 and June 2010. The battery included well-established as well as several newly developed computerized tasks. Sixty-six very preterm children of the original cohort participated, all born before 32 weeks of gestation. In addition, a sample of 66 age-matched term born controls, recruited from the same classrooms or by contacting other schools located in the same area as the schools attended by the very preterm children, was invited to participate in the study. Controls were required to be born after 37 weeks of gestation without any perinatal complications as reported by their parents. Secondly, very preterm children and age-matched term controls were additionally invited to participate in the imaging part of the study, which comprised the use of various imaging techniques, including MRI, DTI, and functional MRI (fMRI). This assessment took part at the VU Medical Center Amsterdam between October 2010 and July 2011.

**Layout of this thesis**

This thesis is divided in three different parts, each directed at one of the three aims. The first part further investigates the nature of problems in motor, cognitive, and behavioral functioning in very preterm children. Whereas the impact of prematurity on cognitive functioning is well-established by existing meta-analyses,[49;51] an accurate prediction of the impact of prematurity on motor skills and their development is lacking. Firstly, a comprehensive meta-analysis on the impact of very premature birth on motor development throughout childhood and adolescence is presented in **chapter 2**. In this meta-analysis, the relations of gestational age, birth weight, and age at motor assessment with motor impairment of very preterm children are explored. Secondly, **chapter 3** and **chapter 4** present the nature of the problems in motor, cognitive, and behavioral functioning of very preterm children at school age. In **chapter 3**, the outcomes of a novel task, measuring visuomotor performance under various circumstances and with increasing workload, is used to study the role of motor planning and online motor control in motor problems of very

preterm children. Whereas **chapter 3** is directed at motor problems, **chapter 4** describes a study investigating the severity and specificity of problems in behavioral functioning in very preterm children, in particular attention problems. Furthermore, this study establishes whether the problems in behavioral functioning of very preterm children are crucially mediated by altered brain functioning, as determined by visual working memory and (consistency in) information processing speed.

The second part addresses alterations in brain development underpinning the functional problems of very preterm children at school age. In order to elucidate the impact of premature birth on brain structure volume development as described in other studies, a meta-analysis was conducted in **chapter 5**. This study provides meta-analytic effect size measures for the impact of premature birth on both grey and white matter structure volumes, as well as several other brain structures including the hippocampus, the cerebellum, and the corpus callosum. In addition, this meta-analysis investigates the role of gestational age, birth weight, and age at assessment, and explores the functional implications of reduced brain structure volumes of very preterm children in childhood. To further elucidate the relations between brain alterations and problems in motor, cognitive, and behavioral functioning, state of the art imaging methods were performed, of which the results are presented in **chapter 6** and **chapter 7**. In both chapters, complementary methods are selected to elucidate the functional differences between altered grey matter development and altered white matter development on the problems in motor, cognitive, and behavioral functioning of very preterm children. **Chapter 6** presents a brain-wide approach including associations between white matter integrity of 18 major white matter tracts (determined using probabilistic fiber tractography), brain structure volumes, and general measures of motor and cognitive development of very preterm children. In addition, the specificity of altered white matter integrity as opposed to altered brain structure volumes, as well as the specificity for motor impairment as opposed to intellectual impairment, is investigated. Furthermore, the potential for using white matter integrity as a predictor for motor problems or DCD status at school age is explored. Supplementary to the brain-wide approach of **chapter 6**, **chapter 7** presents the results of an in-depth method (fMRI-guided diffusion tensor tractography) in order to directly investigate the underlying role of abnormalities in white matter and grey matter development in the brain function of interference control, a core aspect of attention.

In the third part, the potential for improving long term functioning, using nutritional interventions directed at reducing the incidence of serious neonatal infections associated with alterations in brain development, are investigated. In order to elucidate the impact of serious infections on development, a comprehensive meta-analysis was conducted in **chapter 8**. In this meta-analysis, we provide meta-analytic effect sizes for the differences in motor and mental development of very preterm children with and without the presence of serious infections. In addition, differences between various serious infections on developmental outcomes in the first years of life were explored. To investigate whether decreased infectious morbidity following glutamine supplementation improved long term development of very preterm children, we examined differences between the glutamine and placebo group in outcomes of motor, cognitive, and behavioral functioning in **chapter 9**. In addition, to clarify whether decreased infectious morbidity of the glutamine treated group compared to the placebo group, has minimized alterations in brain development, group differences in white matter integrity (as measured using TBSS) and brain structure volumes were examined in **chapter 10**. Importantly, both **chapter 9** and **chapter 10** investigate the mediating role of serious neonatal infections on differences in long term functional outcomes and brain development, respectively. Better growth of very preterm children has been associated with better functional outcomes.[90;91] Finally, **chapter 11** explores the effects of glutamine on growth, by investigating growth trajectories of head circumference, body length, and body weight, from birth up till one year of age. For all very preterm children, data on growth measures were collected during their stay at the NICU, at follow-up assessments at the hospital and outpatient clinic, and during their visits at well-baby centers in the first years of life.

Finally, at the end of this thesis, a summary and discussion of the presented findings can be found. In this discussion, insights from the various studies are combined to progress towards a better understanding of, and ability to intervene on, the complex interaction between altered brain development and functional impairments of very preterm children at school age. This discussion entails a research agenda, providing promising avenues for future research.

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