Imaging the preterm infant's brain

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Chapter 1

General introduction and Outline of the thesis

General introduction

Preterm birth and the immature brain

Preterm birth is an important public health problem. In the Netherlands, each year approximately 14,000 infants are born prematurely at a gestational age (GA) of less than 37 weeks. This represents about 8.0% of all live births. Approximately 2,500 (1.4% of all live births in 2005) of these preterm infants are born very prematurely, at a GA of less than 32 weeks. The incidence of preterm birth has risen over the past decades and is still rising, partly because of the increase in some of the risk factors for preterm birth, including increased maternal age at first birth, more widespread application of fertility treatments, and more multiple pregnancies (1).

Important advances in the care of newborn infants during the past decades have greatly improved the survival and outcome of very preterm infants (GA < 32 weeks). Despite these advances, very preterm infants are still at risk of health problems, both during the neonatal period and later in life. One of the major complications of preterm birth is injury to the brain.

In very preterm infants, important maturational processes of the brain still need to take place after birth (2-9). Very preterm infants spend a long, for brain development critical, period in an incubator on a neonatal intensive- or high-care unit, where undesirable visual and auditory stimuli are superfluous and intense. The clinical condition of most of these infants is unstable, requiring intensive respiratory and/or circulatory support. In addition, they frequently undergo stressful and painful medical and nursing procedures. Many infants need analgesic and/or sedative medication. All these factors may influence and destabilize cerebral blood flow and oxygenation, and thereby increase the risk of brain injury and deviant growth and development.

Brain injury in very preterm infants forms an important problem, not only for the infants but also for the parents, health care and society in general. This is partly related to the large number of these infants who survive with serious neurodevelopmental disability, including cognitive, behavioral, attention or socialization deficits in 25-50% and major motor deficits in 5-10% (8-13). In many very preterm neonates neurological development is delayed and suboptimal in comparison with full-term neonates, even if their age is corrected for prematurity and/or without overt brain injury (14-20).

Neuro-imaging

Imaging the preterm brain during the neonatal period has become an essential, basic part of the modern care of very preterm infants. The two most commonly used and valuable techniques to image the newborn infant's brain are cranial ultrasonography (cUS) and magnetic resonance imaging (MRI). Computed tomography (CT) is nowadays only used under rare circumstances, especially as the radiation dose involved in CT scanning is significant and in most cases it has little or no additional diagnostic value compared to high-quality cUS.

Cranial ultrasonography

cUS was introduced into neonatology as a diagnostic tool in the late 1970s. In short, ultrasound makes use of high-frequency sound waves that are sent into the body by the transducer. The sound waves are reflected at sites of density changes between and within tissues, e.g. between brain white matter (WM) and cerebrospinal fluid. The reflections of the sound waves are returned to the transducer, and processed and transformed into images by the ultrasound machine and software.

Advances in technology over the past decades have improved the quality of cUS imaging, and it is now the preferred technique for imaging the newborn infant's brain throughout the neonatal period and thereafter until closure of the fontanels. cUS can be initiated at a very early stage, shortly after birth, and is the most readily available and easily repeatable tool. It is safe, non-invasive, and can be done at the bedside with little disturbance to the infant. In addition, it is reliable for detecting congenital and perinatally acquired anomalies of the brain and for following brain growth and development (8,14,21-24) (Chapters 2 and 3).

For detailed descriptions on the main aims of cUS imaging in newborn infants, performing a standard high-quality cUS examination through the anterior fontanel, use of additional acoustic windows, and recommendations on timing, see Chapters 2 and 3 of this thesis and the practical guide to 'Neonatal Cranial Ultrasonography' by van Wezel-Meijler (8).

Although the advantages of cUS are numerous and widely appreciated, it also has several limitations that need to be acknowledged. These include that evaluation of superficial structures is often difficult, it is not always possible to precisely define

abnormalities in the cerebellum and posterior fossa, more diffuse and subtle changes may not be well detected, myelination cannot be visualized, and image quality can be affected by small acoustic windows and fluid and/or thick black hair between the transducer and brain. Consequently, there are several indications for (additional) MR imaging in neonates (8) (Chapter 4).

Magnetic resonance imaging

MRI is a relatively new technique that has been used for medical imaging of the structure and function of the body for just over 30 years. It provides detailed images of the body, including its organs and tissues, in different planes. In short, MRI uses a powerful magnetic field to align the hydrogen protons in water molecules, of which the human body mainly consists, in the direction of the field. A radiofrequency pulse is then used to systematically alter the alignment of this magnetization, causing the hydrogen protons to produce a rotating magnetic field that is detectable by the MR scanner. This signal can be manipulated by additional magnetic field pulses to build up enough information to construct an image of (part of) the body.

Since MRI was first introduced into neonatology for imaging the newborn infant's brain, it has greatly contributed to our understanding of brain injury and maturation, and the prediction of neurodevelopmental outcome in both preterm and full-term neonates. Nowadays, MRI is becoming more widely available for clinical imaging, and higher field strength MR systems (1.5 and 3 Tesla), providing higher resolution images, are being used. Consequently, neonatal MR imaging has become increasingly important as a diagnostic tool (4,25-29) (Chapter 4).

MR imaging has several advantages over cUS imaging. MRI demonstrates maturational processes of the brain, and changes therein, in great detail, and is more sensitive for assessing the exact site and extent and the origin of lesions. It thereby helps to define pathological processes and contributes to accurate prediction of outcome in newborn infants. MRI may (additionally) detect abnormalities in areas that are difficult to visualize with cUS, and is generally considered better for detecting diffuse and subtle injury (3-8,24,30-37). Modern MRI techniques, including diffusion-weighted and diffusion-tensor imaging, allow assessment of both the macro- and microstructure of brain structures and tissues, quantification of brain growth and development, and very early

detection of hypoxic-ischaemic injury. In addition, quantitative volumetric analysis, either manually or (semi-)automatically, enable volume measurements of different structures and tissues, including the deep and cortical grey matter (GM), myelinated and unmyelinated WM, and cerebrospinal fluid spaces (32,38-47).

However, although safe, MRI is a more burdening neuro-imaging technique to the sick, very preterm infant than cUS; the infant needs to be transported to and from the MR unit and mostly cannot stay in its own incubator during the examination. This poses challenges regarding patient preparation, monitoring, temperature regulation and safety. Very early imaging, within a few hours of birth, is therefore difficult to realize and, unlike sequential cUS, repetitive MR examinations, particularly to follow brain maturation and the evolution of injury throughout the neonatal period, are undesirable in these vulnerable patients (Chapter 4). Neonatal MR imaging also poses challenges with regard to optimal timing and sequence optimization, partly because of the very high water content of the immature neonatal brain that decreases with ongoing maturation (4,8,29,35,48) (Chapter 4). In addition, some brain findings, including lenticulostriate vasculopathy (LSV), calcification, germinolytic cysts and abnormality of the choroid plexus, are better or only visualized by cUS (33,49).

For all these reasons, cUS and MRI are nowadays mostly considered to be complementary neuro-imaging tools. In very preterm infants, we rely on sequential cUS throughout the neonatal period and a single MRI examination, preferably performed around term equivalent age (TEA). In our hospital, all neonatal MRI examinations are performed according to standard protocols for imaging the newborn infant's brain, which can be adjusted in individual cases based on the infant's clinical course and cUS findings (8) (Chapter 4).

Brain growth and development

Important maturational processes of the brain, including gyration, myelination, cell migration, germinal matrix involution and increase in volume, weight and surface area, take place during the late fetal period and early infancy. As mentioned above, in very preterm infants these processes, normally almost completely (gyration, cell migration) or partially (myelination, brain growth) occurring antenatally, need to take place after birth (2-7).

The maturational processes can be visualized with modern neuro-imaging techniques and show as (age-)specific phenomena on cUS and MRI, changing continuously with age. To distinguish these processes from pathology, it is important for those performing cUS and MRI, and particularly for those assessing the images, to be well informed on normal brain growth and development, on phenomena reflecting maturational processes on cUS and MRI, and on (gestational) age-related patterns of brain injury. In very preterm neonates, this not only includes signal changes on cUS and MRI in brain tissues such as the WM and deep GM and changes in size and structure of the brain over time, but also alterations in brain size and structure in comparison with full-term neonates at equivalent postmenstrual age.

Gyration starts very early, in the second trimester of pregnancy, and continues in an orderly and predictable way, proceeding from the posterior to the anterior parts of the brain. In infants born extremely prematurely (24-26 weeks' GA), the surface of the brain is still very smooth and has a lissencephalic appearance. Gyration is normally completed around term age, when the brain surface has an almost mature appearance. Consequently, in very preterm infants the brain surface before TEA, as depicted by neuro-imaging, differs substantially from that around TEA (4,6,8-9,41,50-55). (Quantitative) MRI studies have shown that very preterm neonates around TEA have less complexity of cortical gyration and reduced cortical GM volumes compared with full-term neonates (38,43,45,47,52).

Like gyration, myelination starts during the second trimester of pregnancy and progresses in an orderly and predictable way, proceeding from the central to the peripheral parts and from the posterior to the anterior parts of the brain. The posterior brainstem is the first structure to become myelinated, while the anterior brainstem, internal capsule and cerebral hemispheres do not start to myelinate until the mid-third trimester. Myelination proceeds rapidly during the late fetal period and infancy, and continues until early adolescence. In very preterm infants, myelination largely takes place after birth (2-5,7-9,41,50,52-53,56). Although myelination is only depicted by MRI and not by cUS, myelination, cell migration and germinal matrix involution do result in changes in the WM that are shown on cUS (8,24).

The germinal matrix is a highly cellular and vascular structure producing neuroblasts and glioblasts. It lines the entire wall of the lateral and 3rd ventricles during early

gestation, and regresses from 24 to 26 weeks onwards. After 34 weeks' gestation, remnants only remain in the caudo-thalamic notch and temporal horns of the lateral ventricles. In very preterm infants before TEA, the germinal matrix can be detected on cUS as small areas of high echogenicity, mostly only around the caudo-thalamic notch, while on T_1- and T_2-weighted MR images it is clearly visible as a respectively high and low signal intensity zone in the ventricular wall (4,8-9,24,41,50,57).

From the first trimester of pregnancy onwards, neurons and glial cells migrate through the WM, from the germinal matrix towards the immature cortex. Neuronal cell migration is complete around 20 weeks' gestation, while migration of glial cells continues until late gestation (second and third trimester) (4,9,57-59). In very preterm infants during the early preterm period, glial cell migration is visible on conventional MR images as bands of alternating signal intensity (4,24,35,41,50,57-62). On cUS, this process may be represented by bilateral, symmetrical areas of subtle increased echogenicity in the frontal and parietal periventricular WM (8,24).

In fetuses and in very preterm infants during the early preterm period, the extracerebral spaces are often wide and the lateral ventricles wide and asymmetrical (predominantly left-sided and occipital horns). Due to brain growth and fluid loss during the first few postnatal days, these spaces gradually become smaller with age (4,8). However, in most preterm neonates around TEA, cerebrospinal fluid spaces are wider in comparison with full-term neonates (9,40,43,45,47,62).

Brain injury

As in very preterm infants brain maturation largely takes place after birth, their brains are vulnerable to injury and deviant growth and development. Brain injury is a major cause of neurological handicaps in very preterm infants (8-13). In addition, in many very preterm infants neurological development is suboptimal, even if corrected for prematurity and/or without overt brain injury (14-20). It can therefore be hypothesized that some forms of cerebral pathology are overlooked or not demonstrated by currently used imaging techniques, that brain growth and/or development is disturbed, and/or that certain phenomena are incorrectly considered normal because they frequently occur in this age-group (32,38,41,43,63).

In newborn infants, the pattern of brain injury varies, depending not only on the origin (i.e. traumatic, ischaemic, hypoglycaemic, inflammatory and/or haemorrhagic) and severity of the insult, but also on the postmenstrual age at the time of the insult. In very preterm infants, the periventricular WM and germinal matrix are the most vulnerable to injury during the perinatal period (9,64).

Early neuro-imaging studies in very preterm infants were mainly directed at the detection of peri- and intraventricular haemorrhage, periventricular haemorrhagic infarction, post-haemorrhagic ventricular dilatation and cystic periventricular leukomalacia (PVL) (27,65-74) (Chapter 2). Over the past decades, the incidence of these abnormalities has decreased and the distribution of WM injury has shifted from cystic and focal lesions to more diffuse and/or subtle changes (9,25,30-31,33,36-37,43,63,75-79). In very preterm infants around TEA, dilatation of the lateral ventricles, widening of extracerebral spaces and decreased complexity of gyration are nowadays frequently reported (9,38,40,42-43,45,47,62). In addition, cUS and MR imaging have improved considerably. Recent studies describing the incidence and evolution of various brain imaging findings in very preterm infants, as detected with modern, high-quality cUS and MRI, are limited.

Identification of risk factors for brain abnormalities in very preterm infants may contribute to appreciating the infants at risk and to early detection and intervention. It may even contribute to prevention of brain injury and neurological sequelae. Previous studies have described risk factors for different forms of injury occurring in the preterm infant's brain (31,77,80-95). However, neonatal care has advanced and the relation between more diffuse and/or subtle forms of WM injury and clinical data is still largely unknown. Recent studies on risk factors for brain abnormalities in very preterm infants throughout the neonatal period are scarce.

White matter

The WM of the cerebral hemispheres predominantly consists of fibres of the cortico-spinal tracts, including descending motor fibres, association fibres and optic radiations. It plays an important role in many functions, including motor control, cognition, behavioural and attention functions, and vision. Injury to and/or deviant growth and development of the WM may therefore lead to significant neurological sequelae, such as spastic motor disorders, cognitive deficits, behavioural and attention deficits, and visual impairment (9).

In the preterm infant's brain, the periventricular WM is largely unmyelinated and has a very high water content. Myelination of the WM starts in the mid-third trimester of pregnancy, and progresses at a high rate until the first months after term age. During the early preterm period, glial cells are still migrating through the WM. In addition, up to the first months after TEA, the volume of the WM increases considerably. Consequently, in preterm infants, the WM changes almost continuously from birth until early infancy (2-5,7-9,41,50,52-53,56-59).

MRI shows these maturational processes in the WM in detail (2-5,7-9,24,41,50,53,57-62). As cUS is the preferred and usually the initial technique for sequential imaging of the preterm infant's brain (8,14,21), it is important to define phenomena that represent normal maturational processes as visualized on cUS.

Bilateral, symmetrical areas of increased echogenicity are frequently encountered on cUS scans of apparently well preterm infants. The areas are mainly located in the frontal and parietal periventricular WM, are less echogenic than the choroid plexus, and do not evolve into obvious lesions. They usually have a linear or smoothly rounded shape. Some of the areas have been correlated anatomically with areas of glial cell migration in the preterm brain before TEA (8,24). It can therefore be hypothesized that these bilateral, symmetrical echogenic areas reflect maturational processes of the immature WM on cUS, comparable to areas of altered signal intensity in the periventricular WM, previously suggested to represent maturational processes, on MRI (4,24,41,50,57-58,60-62).

As mentioned above, in very preterm infants, the distribution of WM injury has shifted from cystic and focal lesions, such as cystic PVL and periventricular haemorrhagic infarction, to more diffuse and/or subtle changes, such as periventricular echodensities (PVE) on cUS and punctate WM lesions (PWML) and diffuse and excessive high signal intensity in the WM (DEHSI) on MRI. Recent studies have focused on the detection and implications of these latter WM changes (9,15,24,30-31,33-34,36-37,62-64,75-79,84,96-99).

Echodensities in the periventricular WM (PVE), also referred to as periventricular flaring, are frequently encountered on cUS scans of very preterm infants, and may represent ischaemic and/or inflammatory damage (9,22,64). PVE are transient, persisting for a variable period of time, and can subsequently resolve or evolve into cystic lesions

(22,24,36). When persisting for more than 7 days, PVE are considered the first stage of PVL (22). PVL often leads to neuronal/axonal injury, affecting not only the WM but also the deep and cortical GM, cerebellum and brainstem (9,64). In preterm infants, cystic forms of PVL have been associated with reduced WM and deep and cortical GM volumes and increased volumes of cerebrospinal fluid spaces around TEA (42-43,47). They often lead to neurological impairment and are mostly well detected by cUS (15,63,100). If long-lasting, milder forms of PVE, not evolving into cysts, may also be associated with suboptimal or deviant neurological development, especially when combined with changes in size and/or shape of lateral ventricles (15,19,33,76,97,99,101). It is important for clinicians to distinguish pathological PVE, especially those leading to neurological sequelae, from phenomena representing maturational processes in the immature WM on cUS (24,102).

Concerns have been raised that cUS is not a good tool for detecting subtle and/or diffuse WM injury, particularly as seen on MRI of very preterm infants around TEA, such as PWML and DEHSI (9,30-31,33,36,62-63,75-76,78-79,98,100,103). PWML show as small areas of high signal on T_1- and low signal on T_2-weighted MR images. They are mostly isolated or linearly in organization and located in the periventricular WM at the level of the centrum semiovale and/or adjacent to the optic radiation (31,75,98). DEHSI shows as areas of excessive high signal intensity diffusely distributed within the periventricular and/or subcortical WM on T_2-weighted MR images (33). These subtle and/or diffuse forms of WM injury have been associated with changes in diffusivity in the WM, with deviant brain growth and development, and with decreased WM and deep and cortical GM volumes and increased volumes of cerebrospinal fluid spaces (25,31,42-43,47,62,80,98). Several authors have attempted to find cUS-correlates for PWML and DEHSI, but so far these have not been established (30,33,36,63,75-76,78-79,100). Although the clinical importance of subtle and/or diffuse WM injury on MRI has not fully been elucidated, preterm infants with this finding seem to be at risk of motor and mental impairment (9,30-31,33,63-64,96-98). The low sensitivity of cUS for subtle and/or diffuse WM injury has prompted several authors to suggest a standard MRI examination in all very preterm infants (63,76,78,100). Recent studies on WM injury in very preterm infants using frequent, sequential high-quality cUS throughout the neonatal period and/or assessing not only changes within the WM but also other brain changes thought to be related to WM injury (such as ventricular dilatation) are limited.

Deep grey matter

The deep GM, i.e. the basal ganglia and thalami (BGT), is important in the guidance of signals to and from other brain structures; all information to and from the cortical GM is guided through and modulated by the thalamus (9,64). Consequently, the deep GM plays an important role in many functions, including motor control, cognition, affective functions and vision. Injury to and/or deviant growth and development of the deep GM may therefore lead to significant neurological sequelae, such as motor problems, cognitive deficits, affective deficits and visual impairment (9).

The basal ganglia consist of the caudate nucleus and lentiform nucleus, which is subdivided into the globus pallidus and putamen. The caudate nucleus, lentiform nucleus and thalamus are separated by the anterior and posterior limbs of the internal capsule (104). Myelination of the deep GM starts early, at the beginning of the third trimester of pregnancy. It then progresses rapidly throughout the different areas of the deep GM until 3 months post-term. Consequently, in preterm infants, the deep GM changes almost continuously from birth until maturation is complete (2,4-5,7,56).

MRI shows the maturational processes in the deep GM in detail, as has been described by several authors (2-5,7,61). However, albeit less detailed, cUS may also show maturational processes in these structures in very preterm infants (72,105). Although, so far, this has received little attention, it is important to define phenomena that represent normal maturational processes of the immature deep GM as visualized on cUS in very preterm infants, and to distinguish these from pathological processes.

Echogenicity of the BGT region (EG-BGT) is frequently encountered on cUS scans of very preterm infants and fetuses. EG-BGT is mostly seen as bilateral, subtle and diffusely increased echogenicity in the BGT region in comparison with surrounding tissue. Its origin and clinical significance in both preterm infants and fetuses are largely unclear (72,105-106). It can be hypothesized that EG-BGT, like the bilateral, symmetrical echogenic areas in the frontal and parietal periventricular WM mentioned above (24,102), represents a normal maturational phenomenon of the immature deep GM. However, like mostly more distinct, demarcated and often more inhomogeneous echodensities in the BGT in (near) full-term neonates (107-109), it may also reflect ischaemic and/or inflammatory damage and be of clinical importance.

Injury to the deep GM seems relatively infrequent in very preterm infants. The main forms of injury to the BGT include localized lesions that are unilateral or bilateral and mostly reflect infarction of the lenticulostriate branches of the middle cerebral artery and haemorrhage. They have been associated with suboptimal neurodevelopmental outcome (19,110-114). The incidence of these focal lesions in preterm infants seems low, with incidences reported up to 5% for cUS and up to 8% for MRI, and they appear to resolve before TEA (19,31,33,105-106,111,115-117).

Another, more frequent localized finding in the deep GM of very preterm infants is LSV. LSV is depicted by cUS as an unilateral or bilateral punctate, linear or branching echogenic structure in the distribution of the thalamo-striatal vessels. It has been associated with a wide variety of clinical conditions of the fetus and neonate, including congenital (e.g. TORCH) and acquired neonatal infections, chromosomal abnormalities, congenital heart disease, other congenital malformations, hypoxic-ischaemic events, and metabolic disorders (23,49,118-135). In addition, it occurs more often in infants of multiple pregnancies, particularly monochorionic twin pregnancies, than of singleton pregnancies and in full-term neonates than in preterm neonates (123,126,136-138). However, the incidence, aetiology and clinical significance of LSV in very preterm infants are largely unclear, and so far no MRI-correlate has been established (121,123,127).

Finally, recent studies have described visually and quantitatively assessed reductions in deep GM volumes in preterm neonates around TEA in comparison with full-term neonates, being more prominent in case of WM injury (31,39,43,46,64,115,139-141). However, neuro-imaging data on growth and development of the deep GM, and their relation with WM injury, in very preterm infants are limited (43,46,115).

Outline of the thesis

The general aim of this thesis is to study and describe brain imaging findings in very preterm infants, including normal maturational phenomena as well as pathological changes, using modern, high-quality imaging techniques.

This thesis reports the results of 11 reviews and original studies on neuro-imaging in (very preterm) neonates and is divided into six parts. Except for the study in Chapter

7, which was performed at the Hammersmith Hospital, London (United Kingdom), all studies were performed at the tertiary neonatal referral centre of the Leiden University Medical Center, Leiden (the Netherlands), and restricted to the population of infants born very prematurely (GA < 32 weeks). We selected this population as very preterm infants are the most at risk of experiencing brain injury, and are a relatively homogeneous group with respect to the occurrence of brain injury and severity of illness. Besides the studies reported in Chapters 8 and 10, all studies had a prospective design and were performed in large (consecutive) cohorts of very preterm infants.

Part II reviews the techniques used to image and follow the newborn infant's brain during the neonatal period.
Chapters 2 and 3 discuss our experience on neonatal cUS imaging and address issues on technical aspects, appropriate timing and protocols, diagnostic accuracy, safety, and optimizing its performance.
Chapter 4 discusses our experience on neonatal MR imaging and addresses its indications, technical aspects and sequences, appropriate timing and protocols, safety, and patient preparation and transportation.

Part III gives an overview of brain imaging findings in very preterm infants.
Chapter 5 describes the incidence and evolution of brain imaging findings, assessed with frequent, sequential cUS throughout the neonatal period and MRI around TEA. The accuracy of both techniques is compared for findings seen around TEA.
Chapter 6 reports the relation between frequent and/or clinically relevant brain imaging findings during the early neonatal period and around TEA and several potential perinatal risk factors. It is evaluated whether risk factors have changed over recent decades.

Part IV focuses on imaging of the WM in very preterm infants.
Chapter 7 describes the incidence and origin of bilateral, symmetrical and subtle echogenic areas in the frontal and parietal periventricular WM, frequently seen on cUS scans of apparently well preterm infants. cUS scans are compared with contemporaneous T_2-weighted MR images to identify MR-correlates for these cUS phenomena.

Chapter 8 assesses the value of sequential, neonatal cUS and MRI within the first 3 months after birth for detecting WM changes, and for predicting short-term neurodevelopmental outcome based on WM changes.
Chapter 9 evaluates the reliability of a classification system for grading WM injury, based on a combination of findings in the WM and abnormality of lateral ventricles on frequent, sequential cUS throughout the neonatal period, using a MRI classification system as reference standard.

Part V focuses on imaging of the deep GM in very preterm infants.
Chapter 10 assesses the incidence, clinical significance and origin of bilateral, subtle and diffusely increased echogenicity in the basal ganglia and thalami (EG-BGT), frequently seen on cUS scans of very preterm infants. EG-BGT is related to findings in the deep GM on MRI and to short-term neurological outcome.
Chapter 11 systematically describes imaging findings of the deep GM, and their relation with age and WM injury, assessed with sequential, neonatal cUS and MRI around TEA. The incidence and characteristics of EG-BGT and its relation with other brain imaging findings and quantitative measurements of the deep GM are studied. Additionally, the relation between quantitative measurements of the deep GM, indicative of growth and development, and age and WM injury is assessed.
Chapter 12 studies the incidence, evolution and clinical significance of LSV, as seen on frequent, sequential cUS throughout the neonatal period. LSV is related to perinatal clinical parameters, previously associated with brain injury in preterm infants, and to findings in the deep GM on MRI.

Part VI
Chapter 13 gives an overview of the main findings and conclusions of the reviews and original studies reported in this thesis, and discusses future perspectives and proposals for further research.
A summary in English is presented in **Chapter 14**, and a summary in Dutch in **Chapter 15**.

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