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Summary
The general aim of this thesis is to assess the diagnostic and predictive value of MRI in imaging the preterm infant’s brain.

In May 2006 a prospective study was started including very preterm infants with a gestational age <32 weeks, admitted to the neonatal intensive care unit of the Leiden University Medical Center. Bedside cranial ultrasound examinations were performed following a standard routine and 113 of these infants underwent an MRI examination preferably performed at term equivalent age. Ethical approval for the study was given by the institutional review board and informed consent was obtained for each infant. All MRI examinations were performed using a standard protocol for imaging the newborn infant’s brain, using a 3.0 T MRI system (Philips Medical Systems, Best, the Netherlands).

Chapter 2
In the second chapter we review the literature regarding radiological assessment of white matter injury in very preterm infants. We discuss the imaging findings on cranial ultrasound and MRI, and the imaging modalities and techniques used to depict white matter injury. The use and utility of advanced techniques such as diffusion tensor imaging, volumetric and segmentation techniques, magnetization transfer imaging, functional resting state MRI, as well as MR spectroscopy are discussed.

Chapter 3
This chapter focuses on diffusion tensor imaging and fibre tractography. We performed these techniques to study the developing white matter tracts of the internal capsule and corpus callosum around term equivalent age in our cohort of very preterm infants. The aim of the study was to establish the association between DTI parameters and age, white matter injury and clinical factors. We found associations between FA and ADC values and postmenstrual age at imaging, indicative of developing white matter. However, we did not find associations between DTI parameters and gestational age, white matter injury categorized as mild, moderate or severe, or clinical factors.

Chapter 4
The aim of the study described in this chapter was to investigate whether tractography of white matter tracts performed at term equivalent age independently predicts neurodevelopmental outcome at two years of age in very preterm infants. We found associations between lower FA values in the posterior limb of the internal capsule and psychomotor delay and cerebral palsy, and also an association between higher ADC values in the splenium of the corpus callosum and psychomotor delay, independent of white
matter injury, ventricular dilatation and clinical factors. These observations confirm that DTI tractography at term equivalent age can independently predict psychomotor delay and cerebral palsy at two years of age.

Chapter 5
The research question in this study was whether cranial ultrasound performed in the perinatal period can reliably predict diffuse white matter injury as seen on MRI performed around term equivalent age. A classification for white matter injury was used for both imaging modalities. The predictive value of the cranial ultrasound classification for white matter injury on MRI was calculated. There was a reasonably high positive predictive value for detection of severe white matter on MRI, but to a lesser extent for mild or moderate white matter injury, prompting the indication for an MRI examination at term equivalent age to detect diffuse white matter injury.

Chapter 6
As diffuse white matter injury is not well detected by cranial ultrasound, our aim was to assess the predictive value of individual abnormalities on cranial ultrasound for white matter injury on MRI around term equivalent age and neurological outcome. Periventricular echo densities in the white matter on cranial ultrasound reasonably predict mild, moderate and severe white matter injury observed on term equivalent age MRI. They also predict the occurrence of diffuse excessive high signal intensity (DEHSI) on MRI. However, absence of periventricular echo densities does not predict absence of white matter injury or DEHSI on MRI. No associations existed between inhomogeneous periventricular echo densities and focal punctate white matter lesions on MRI. Peri and intraventricular hemorrhages were highly predictive of abnormal white matter on MRI and also, together with ventricular dilatation, reasonably predictive of an unfavorable outcome at two years. Absence of cranial ultrasound abnormalities in the white matter and normal ventricular size and shape are highly predictive of a normal outcome at two years.

Chapter 7
In the study described in this chapter we investigate the clinical implications of individual MR imaging findings in the white matter on MRI at term equivalent age in terms of neurodevelopmental outcome at two years. The most important finding was that DEHSI, which occurred in the majority of infants imaged at term equivalent age showed no association with an abnormal neurologic outcome. We therefore postulated that DEHSI represents a prematurity related developmental phenomenon rather than white matter
injury. Furthermore punctate white matter lesions and ventricular dilatation were associated with mental and psychomotor developmental delay and cerebral palsy.

Chapter 8
The study described in this chapter demonstrated that cerebellar hemorrhage in the very preterm infant is a frequent finding and, using ultrasound, it is better diagnosed using the mastoid fontanelle approach in addition to routine cranial ultrasound through the anterior fontanelle. Gradient echo MRI, used as a reference standard demonstrated more (punctate) hemosiderin deposits not diagnosed on cranial ultrasound. We concluded that the predictive implications of these smaller lesions needed further attention.

Chapter 9
In this chapter we studied the clinical value of gradient echo MRI detecting small punctate hemosiderin deposits in relation to neurodevelopmental outcome at two years. Presence of small hemosiderin deposits in the ventricular wall correlated with white matter injury on MRI around term equivalent age and with a lower psychomotor developmental index at two years. However, after correction for gestational age, white matter injury and clinical factors, this correlation was no longer significant. We concluded that the importance of detecting small hemosiderin deposits using gradient echo MRI is limited as there is no independent association with neurodevelopmental outcome.

Concluding remarks and future perspectives
The aim of this thesis was to investigate the diagnostic value of MRI performed at term equivalent age in terms of detecting brain injury and predicting neurodevelopmental outcome in very preterm infants (gestational age <32 weeks).

In these patients, MRI is a powerful tool to diagnose all types of white matter injury, while cranial ultrasound can detect hemorrhages, ventricular dilatation and cystic white matter lesions. MRI is sensitive in detecting punctate white matter lesions, which are associated with mental and psychomotor delay and cerebral palsy at follow up. White matter echo densities on ultrasound in the neonatal period do not correlate with these punctate white matter lesions on MRI around term equivalent age. Although MRI is a sensitive technique for detecting white matter lesions in general, the positive predictive value of specific MRI findings such as punctate white matter lesions, and also cystic lesions and ventricular dilatation for cognitive and motor delay is low.

Currently conventional MRI can predict that a very preterm infant will have a nor-
mal or abnormal outcome with a reasonable certainty, when the MRI examination either shows no focal white matter lesions and volume loss or when there is severe white matter damage, post hemorrhagic ventricular dilatation and volume loss. However, the outcome of very premature infants with mild or moderate white matter injury is still uncertain. As normal cranial ultrasound also is highly predictive for normal outcome, routine clinical MRI in every preterm infant at term equivalent age does not seem warranted. Long-term clinical follow up does remain necessary to further evaluate the predictive values of individual neuro-imaging findings and quantitative values around term equivalent age for cognitive neurodevelopmental outcome in very preterm infants.

An advanced MRI technique such as DTI is promising, and, as demonstrated in several of our studies, may help predicting clinical outcome. However, when the findings on the conventional MRI sequences are also taken into account, there is only a slight increase in sensitivity and specificity using DTI. Therefore there still is no indication for the routine use of DTI in daily clinical practice. The same is true for other advanced techniques such as volumetric and segmentation techniques, the use of which is not yet feasible in a clinical setting. Also the relation with neurodevelopmental outcome has not been studied extensively. Whole-brain statistical methods developed for DTI analysis, such as tract-based spatial statistics and atlas-based analysis might have the potential to detect mild-to-moderate white matter injury in relation to neurological outcome. Other advanced techniques such as functional resting state MRI and magnetization transfer imaging are still under active investigation. Additional research is needed to determine the clinical utility of these advanced techniques and their potential to reveal the anatomical substrate for cognitive deficits in preterm infants who do not appear to have abnormalities on other imaging techniques. In the future, serial MRI with combined grading and the application of newer techniques may provide insights into brain development and injury to the preterm infant’s brain, and they may help predicting neurological outcome.