General Introduction
A young girl comes to our outpatient clinic for her follow-up visit at 8 years of age. As a neonate, she was treated with extracorporeal membrane oxygenation for severe meconium aspiration syndrome. Upon discharge, her cranial ultrasound was normal and routine visits in the first years of life showed favourable outcomes. In her records we see that on her routine IQ assessment at 5 years of age, she scored well-above average. She is a bright young girl, plays sports and is healthy. However, when asked how she is doing, she starts to cry. She says she keeps forgetting the plans she has made with friends or the homework she has to turn in the next day. She is in tears because she fears people will think she is not smart. Her parents are worried, they also question what will happen when she has to make the transition from primary school to high school. They do not understand what is wrong with her…

The number of critically ill neonates surviving after neonatal intensive care admission is increasing worldwide. The girl described here is, unfortunately, not unique. It is therefore of utmost importance that our focus broadens from prevention of mortality to long-term outcome in critically ill neonates.

A clearly delimited group of survivors of neonatal critical illness are children treated with neonatal extracorporeal membrane oxygenation (ECMO) or congenital diaphragmatic hernia (CDH) treated without ECMO. Since the first neonatal ECMO treatment applied in 1975, nearly 40,000 neonates have been treated with ECMO worldwide. The annual number of neonatal ECMO runs has decreased over the years and there has been a shift from respiratory to cardiac runs. Nonetheless, the most frequent underlying diagnoses for neonatal ECMO remain meconium aspiration syndrome (MAS) and congenital diaphragmatic hernia (CDH). The survival rate following MAS is over 90%. CDH is a rare congenital anatomical malformation associated with significant mortality and morbidity due to pulmonary hypoplasia and pulmonary hypertension. In the most severe cases of CDH, patients require treatment with ECMO and mortality rates are 49%. Over the past decade, standardized treatment protocols for CDH patients have led to less need for ECMO and to lower mortality rates.

The assessment of long-term outcome in these children is therefore increasingly important. Of particular concern is the neuropsychological outcome following neonatal critical illness. The brain is rapidly developing during the first months of life and therefore particularly vulnerable in these children. Given the importance of neuropsychological functioning both for academic performance and daily life activities, it is imperative to correctly identify and treat survivors of neonatal ECMO and/or CDH at risk of such long-term impairments.
IDENTIFICATION OF PATIENTS AT RISK

Neuropsychological assessment

Within the last decade, a number of studies have evaluated long-term neuropsychological outcome following neonatal ECMO and/or CDH. Fortunately, a significant number of children survive without overt neurological abnormalities, such as haemorrhage or periventricular leukomalacia. Moreover, general cognitive outcome seems generally comparable to that of healthy children at various stages of development. Strikingly, however, the incidence of school problems is significantly higher in these children compared to the general population. This is highly suggestive of an alternative explanation related to specific neuropsychological deficits rather than general intellectual functioning.

A limited number of follow-up studies have assessed specific neuropsychological functions in neonatal ECMO and/or CDH survivors. Sustained attention has been evaluated in 8-year-old survivors of CDH, both in patients treated with and without ECMO. Attention deficits were found in 68% of children compared to the general population, with no influence of treatment type. In 8-year-old neonatal ECMO survivors following CDH as well as other diagnoses, sustained attention deficits were found as well, while visual-motor integration was normal. In the UK ECMO Trial, verbal and visual memory were assessed in 7-year-old survivors of severe respiratory failure randomized to receive either neonatal ECMO or conventional management. Both groups had significantly worse verbal and visual memory compared to the norm. Taken together, these studies suggest both memory and attention deficits following neonatal critical illness, while intelligence and visual-motor integration are normal. However, neuropsychological assessment including all major cognitive domains in the same cohort is lacking. As such, the domains most affected following neonatal ECMO and/or CDH remain largely speculative. To improve identification of patients at risk, clear delineation of the neuropsychological profile following neonatal ECMO and/or CDH is needed.

Neuroimaging

It is crucial to identify patients at risk of school problems as early as possible. Illness and treatment characteristics, such as underlying diagnosis or the duration of mechanical ventilation, may be useful to predict neuropsychological impairments as early as in infancy. However, as of yet, results have not been conclusive. Severity of illness rather than independent clinical characteristics may increase a child’s risk of long-term impairments, but quantifying severity of illness is difficult and clinically useful risk factors remain unknown. Therefore, it is important to investigate alternative ways to improve early identification. The use of advanced neuroimaging techniques to parcellate specific neurobiological correlates of impaired outcome may be useful in this respect. Studies
utilizing sophisticated neuroimaging methods to study survivors of neonatal ECMO and/or CDH are scarce.\textsuperscript{14,15} Van den Bosch et al. showed cortical thickness and global brain volumes in 8-to-15 year-old neonatal ECMO survivors to be similar to healthy controls, despite verbal memory problems in survivors.\textsuperscript{15} These results suggest that the underlying brain injury in ECMO survivors may be more specific and/or subtle. In school-age children who experienced neonatal hypoxia, specific alterations in bilateral hippocampal volume were found compared to healthy controls, which were associated with memory deficits in patients.\textsuperscript{9} In preterm infants, hippocampal volume measured at term-equivalent age correlated with memory outcomes both at two years and seven years of age.\textsuperscript{16,17} These findings indicate a potential predictive value of MRI. The neurobiological alterations associated with long-term neuropsychological deficits are therefore of interest, but remain unknown in survivors of neonatal ECMO and/or CDH.

**TREATMENT OF PATIENTS AT RISK**

Given the increased risk of neuropsychological impairments and school failure following neonatal ECMO and/or CDH, it is essential to find ways to prevent or diminish impaired outcome. However, few such intervention strategies are available. Cognitive training programs are based on the idea that repetitive mental exercise of one cognitive task results in improved functioning that may generalize to other tasks with similar underlying skills. A widely evaluated cognitive training for children with working-memory problems is Cogmed Working-Memory Training (CWMT).\textsuperscript{18} In children born preterm or with ADHD, studies have demonstrated near- and, although to a lesser extent, far-transfer effects after CWMT, i.e. improvements on trained and untrained cognitive functions.\textsuperscript{19,20} As working-memory is one of the fundamental building blocks for higher cognitive functioning and highly associated with academic performance, CWMT may be beneficial for survivors of neonatal ECMO and/or CDH.\textsuperscript{21} However, its effectiveness remains unstudied in these children.

**AIMS AND OUTLINE OF THIS THESIS**

Growing up after neonatal ECMO and/or CDH has long-term neurodevelopmental consequences.\textsuperscript{10,11,13-15} Therefore, long-term follow-up is of great importance in these children. Neuropsychological follow-up after neonatal critical illness should have two main objectives: 1) (early) identification of patients at risk; 2) improving neuropsychological outcome in patients at risk. This thesis addresses these objectives (Figure 1).
Identification. The specific neuropsychological profile and its underlying neurobiology remain largely unknown – knowledge that is essential in order to improve (early) identification of patients at risk. First, the specific neuropsychological profile following neonatal ECMO and/or CDH is delineated, from infancy to school-age (chapters 2 & 3) and into adolescence (chapter 4). Secondly, the neurobiology following neonatal ECMO is compared to healthy controls using advanced neuroimaging techniques (chapter 5), and the associations between brain alterations and long-term neuropsychological deficits are investigated in survivors of neonatal ECMO and/or CDH (chapter 6). Lastly, the pathophysiology underlying the brain alterations and associated long-term neuropsychological deficits across survivors of common causes of neonatal critical illness is explored by reviewing the literature (chapters 9 & 10).

Treatment. In addition to reliable and early identification of patients at risk, there is a need for treatment modalities or intervention strategies to improve neuropsychological outcome in these children. Therefore, the effects of a cognitive training program on neuropsychological outcome (chapter 7) and brain connectivity (chapter 8) in school-age survivors of neonatal ECMO and/or CDH are studied.

Finally, the results of the studies are placed in a broader perspective and aims for future research are described (chapter 11).

---

**Figure 1.** A schematic overview of the contents of this thesis
REFERENCES


