

<http://hdl.handle.net/1765/105797>

Summary

Introduction

Children growing up after neonatal critical illness are at risk of long-term neuropsychological deficits and school problems. However, the specific neuropsychological profile and its underlying neurobiology have remained largely unknown. Furthermore, strategies to prevent or diminish impaired outcome have remained unstudied. These knowledge gaps are tackled in a clearly delimited group of survivors of neonatal critical illness: children treated with neonatal extracorporeal membrane oxygenation (ECMO) and children with congenital diaphragmatic hernia (CDH) treated without ECMO.

Cognition and the brain after neonatal critical illness

In **chapter 2**, the developmental trajectory of IQ in survivors of neonatal ECMO is described at the ages of 2, 5, and 8 years. We show that IQ is stable and average in these children. Despite average IQ, neonatal ECMO survivors are more often in need of extra help in school compared to the general population. Specific neuropsychological deficits may be underlying these school problems. Indeed, we show that increased need for help in school is associated with sustained attention deficits, irrespective of IQ. We further demonstrate that children with CDH who needed ECMO treatment are at highest risk of long-term neuropsychological deficits.

In **chapter 3**, we use elaborate neuropsychological assessment to assess the neuropsychological outcome profile following neonatal ECMO and/or CDH at 8 years of age. Despite a generally average IQ, we show significant deficits in sustained attention, and short- and long-term verbal and visuospatial memory in survivors of neonatal ECMO and/or CDH compared to the general population. We find that children with CDH who needed ECMO have lower IQ than those not treated with ECMO and those treated with ECMO following diagnoses other than CDH. However, the specific neuropsychological deficits are similar across these groups. We also explore potential risk factors of long-term neuropsychological deficits. Our results show that a higher maximum vasoactive-inotropic score (maximum dose of vasoactive medication required during hospital stay) is specifically associated with long-term verbal and visuospatial memory deficits at 8 years of age. These findings may indicate a relationship between early cerebral hypoperfusion and memory in later life.

In **chapter 4**, we assess neuropsychological outcome in 17-year-old survivors of neonatal ECMO. We find similar deficits as those found at 8 years of age. Adolescents have significantly worse short- and long-term verbal and visuospatial memory compared to the norm. Sustained attention is not assessed at this age. These findings suggest memory deficits to persist until adolescence following neonatal ECMO.

In **chapter 5**, Diffusion Tensor Imaging and structural MRI are used to compare white matter microstructure and hippocampal volume between neonatal ECMO survivors and healthy controls (8-15 years). We find that neonatal ECMO survivors have significantly lower global fractional anisotropy, a measure of coherence of white matter fibers, which may indicate long-term injury to neural tracts. In addition to these global differences, we find significantly lower fractional anisotropy in the cingulum bundle, and higher mean diffusivity – suggestive of decreased integrity in axonal membranes, packing, or myelin – in the parahippocampal part of the cingulum. Furthermore, we show smaller hippocampal volume in neonatal ECMO survivors compared to controls, which is associated with worse verbal memory in these children. These results help define the underlying neurobiology involved in the long-term neuropsychological deficits following ECMO.

In **chapter 6**, we assess whether the neuropsychological deficits observed following neonatal ECMO are specifically associated with the brain alterations described in chapter 5. In a different cohort of survivors of neonatal ECMO and/or CDH (8-12 years), we show that lower global fractional anisotropy and lower fractional anisotropy in the cingulum bundle are associated with sustained attention deficits. Higher mean diffusivity in the parahippocampal part of the cingulum is associated with visuospatial memory deficits, whereas smaller hippocampal volume is associated with verbal memory deficits. Our findings indicate specific neurobiological correlates of attention and memory deficits in school-age survivors of neonatal ECMO and CDH. The structure-function relationships are observed irrespective of diagnosis or type of ECMO-cannulation. Interestingly, our results are in line with findings in survivors of other types of critical illness in early life, such as neonatal hypoxia and congenital heart disease.

Can we train the damaged brain after neonatal critical illness?

In **chapter 7**, we describe neuropsychological functioning immediately and one year after Cogmed Working-Memory Training (CWMT), assessed using a nationwide, single-blind randomized controlled trial in school-age (8-12 years) survivors of neonatal ECMO and/or CDH. In children trained with CWMT, we find immediate improvements in verbal and visuospatial working-memory compared to non-trained controls. However, these improvements do not persist until one year post-intervention. Sustained improvements in long-term visuospatial memory in the CWMT group are found one year post-intervention compared to the non-training group. Given the high risk of visuospatial memory deficits in this population, CWMT may be beneficial for survivors of neonatal critical illness with these specific deficits.

In **chapter 8**, white matter microstructure assessed using Diffusion Tensor Imaging is compared between school-age (8-12 years) neonatal ECMO and/or CDH survivors im-

mediately after CWMT and compared to non-trained survivors. We find training-induced changes in both global white matter microstructure as well as in the left superior longitudinal fasciculus in the CWMT group compared to non-trained children. Increased fractional anisotropy in the superior longitudinal fasciculus is significantly associated with improved verbal working-memory in the CWMT group. However, the global increase in fractional anisotropy is not associated with any cognitive improvements. Nonetheless, our findings demonstrate neuroplasticity following neonatal ECMO and/or CDH. Future studies that include neuroimaging and neuropsychological assessment both immediately and one year post-intervention are needed.

The vulnerable brain in critically ill infants

In **chapter 9**, we describe the results of a comprehensive literature review on memory and its neurobiological substrates, specifically the hippocampus, in children following preterm birth, congenital heart disease, neonatal ECMO treatment and/or CDH. We propose a common neurodevelopmental pathway following neonatal critical illness where early hippocampal alterations are associated with memory deficits later in life across survivors of neonatal critical illness, irrespective of underlying diagnosis or gestational age. We suggest that this shared hippocampal vulnerability is probably related to common conditions associated with neonatal critical illness, including hypoxia, neuroinflammation, stress, exposure to anesthetics, or a complex interplay of these factors at different postconceptional ages. The clinical implications of these findings and future perspectives are discussed.

In **chapter 10**, we describe the results of a literature review on the effects of commonly used analgesics and sedatives (analgo-sedatives) on the brain and neuropsychological outcome in critically ill neonates. Infants admitted to neonatal or pediatric intensive care units receive very high amounts of these drugs, which may contribute to the neurodevelopmental impairments observed in these children. Although less obvious in human studies than animal studies, results indicate that exposure to analgo-sedatives in neonates and infants may have long-term effects on the brain and cognition. Specifically, the hippocampus and memory may be affected by sedatives such as midazolam and propofol. A balanced approach that includes the assessment and quantification of both wanted effects and unwanted effects of analgo-sedatives is needed. Therefore, long-term neuropsychological outcome should be assessed as well when evaluating drug efficacy and safety.

In **chapter 11**, we discuss our main findings, compare them with the current literature and make recommendations for future research to improve long-term outcome following neonatal critical illness. Our findings emphasize the need for long-term neuropsychological

logical follow-up in these patients and the need for early identification of patients at risk for long-term neuropsychological deficits and school problems. As MRI is a non-invasive technique, using hippocampal volume in early infancy as a neurobiological marker of memory deficits in later life may in the future lead to earlier identification of patients at risk. Longitudinal studies in which neurodevelopment is assessed using both neuroimaging and neuropsychological assessment are therefore imperative following neonatal critical illness, favorably using a healthy control group. Furthermore, an important area of future research is to gain insight into the exact pathophysiological mechanisms. This insight may lead to diminished or even prevention of long-term adverse outcomes by adjustments in neonatal critical care and/or application of neuroprotective strategies. Intervention strategies that aim to improve impaired neuropsychological outcome at a later stage in survivors of neonatal critical illness remain of interest as well. Assessing the effectiveness of multimodal interventions, such as cognitive training combined with an exercise program, may be beneficial in survivors of neonatal critical illness. Finally, to improve outcome following neonatal critical illness in current practice, providing psychoeducation, compensatory techniques and external (aids) should become a standard part of (long-term) care following neonatal critical illness.