Memory deficits following neonatal critical illness: a common neurodevelopmental pathway

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SUMMARY

Over the last decade, knowledge has emerged that children growing up after neonatal critical illness, irrespective of underlying diagnosis, are at risk of memory impairment and school problems. Strikingly, these problems are manifest even when intelligence is normal. In this review, we propose a common neurodevelopmental pathway following neonatal critical illness by demonstrating that the survivors of preterm birth, congenital heart disease, and severe respiratory failure, share an increased risk of long-term memory deficits and associated hippocampal alterations. Rather than being a consequence of underlying diagnosis, we suggest that this shared vulnerability is most likely related to common conditions associated with neonatal critical illness. These include hypoxia, neuroinflammation, stress, exposure to anaesthetics, or a complex interplay of these factors at different postconceptional ages. Future work should be aimed at improving early identification of patients at risk and evaluating intervention modalities, such as cognitive or exercise training.

INTRODUCTION

Over the last decade, the number of children admitted to neonatal intensive care units has increased significantly worldwide.[1,2] Due to medical improvements, the majority of these children now survive to discharge[1,2], necessitating our focus to broaden from prevention of mortality to long-term outcome. Fortunately, a significant number of children survive without overt brain abnormalities, such as cerebral haemorrhage or periventricular leukomalacia.[3-5] However, knowledge has emerged that children growing up after neonatal critical illness, irrespective of gestational age or underlying diagnosis, are at risk of neuropsychological impairments and school problems. Strikingly, these problems exist even when intelligence is within the average range.[6-9]

Memory deficits are frequently reported following neonatal critical illness. The hippocampus is the critical hub for memory formation.[10] Interestingly, the hippocampus is particularly vulnerable to conditions associated with critical illness, such as hypoxia and neuroinflammation.[11,12] We therefore speculate that a common neurodevelopmental pathway exists across critically ill neonates, where early hippocampal alterations result in long-term memory deficits. This 'growing into deficit' phenomenon[13] – where subtle brain injuries acquired in early life only become evident later in life when those brain regions are required for higher cognitive functioning – can potentially be delineated following three major causes of neonatal critical illness: preterm birth, congenital heart disease (CHD), and severe respiratory failure (necessitating neonatal extracorporeal membrane oxygenation (ECMO) treatment).

In this review, we describe the abnormalities in long-term memory functioning, and summarize findings on memory and its neurobiological substrates, specifically those pertaining to the hippocampus, in children following preterm birth, CHD and neonatal ECMO treatment. Next, we evaluate why the hippocampus may be particularly vulnerable in these children. Taken together, we propose a common neurodevelopmental pathway following neonatal critical illness. We conclude with the potential clinical implications and future directions of research.

SEARCH STRATEGY AND SELECTION CRITERIA

PubMed was searched for articles published between January 1, 2000 and June, 2017 with the search terms in the title or abstract: ("brain imaging" OR "brain" OR "neuroimaging" OR "magnetic resonance imaging" OR MR* OR hippocamp* OR "limbic") AND ("memory" OR "learning") AND (("preterm" OR "preterm birth" OR "premature birth") OR ("congenital heart disease" OR complex heart anomal* OR "complex heart disease") OR ("neonatal respiratory failure" OR "acute respiratory failure" OR "neonatal extracorporeal membrane oxygenation"

OR "neonatal ECMO")). This search resulted in 348 references. We reduced the number to 258 by restricting findings to human studies. Studies that did not assess the hippocampus specifically and/or did not assess memory, and studies including patients with severe neurologic abnormalities or genetic syndromes known to affect neurodevelopmental outcome were excluded. Searches were supplemented by hand searching of reference lists of published articles. The final reference list was generated on the basis of relevance to the scope of this review. In total, 27 studies were included.

MEMORY AND THE HIPPOCAMPUS FOLLOWING NEONATAL CRITICAL ILLNESS

Despite generally average intelligence, the incidence of academic difficulties is strikingly high following preterm birth, CHD and severe respiratory failure.[6,7,9,14-16] This is highly suggestive of an alternative explanation related to specific neuropsychological deficit rather than general intellectual functioning (Table 1). Memory deficits can greatly affect daily activities and academic achievement, and have been reported in 19-41% of children born preterm[7,19], in 28-64% of children with CHD[20], and in 50-70% of children with severe respiratory failure, treated with or without neonatal ECMO[18], compared to 16% in the general population.[17] These deficits become particularly evident as children get older, suggesting that they 'grow into their deficits'.

Table 1. Neuropsychological impairments following neonatal critical illness

	IQ	Attention	Verbal memory	Visuospatial memory	Executive functioning	Visuospatial processing	Academic difficulties
Preterm	x	x	x	x	x	x	x
CHD		x	x	?	x	x	x
Neonatal ECMO[1]		x	x	x	*		x
CDH		x	x	x			x

Frequently reported neuropsychological impairments following neonatal critical illness, an impairment regarded to be significantly lower than healthy controls. In case of intelligence (normal mean IQ(SD) = 100(15), reported mean IQ score of ≤ 85 (i.e. ≤ -1 SD) is regarded impaired.

[1]Neonatal ECMO treatment applied in case of severe respiratory failure, such as meconium aspiration syndrome or congenital diaphragmatic hernia.

*Only working-memory impairments.

? Indicates equally impaired and normal outcomes reported in studies.

Abbreviations: IQ, intelligence quotient; CHD, congenital heart disease; ECMO, extracorporeal membrane oxygenation; CDH, congenital diaphragmatic hernia.

Memory encoding, consolidation and retrieval are highly dependent on the hippocampus and its connections, which are embedded within the brain's limbic system.[10] The hippocampus is thought to be highly involved in the ability to store and retrieve information about an event as well as about the context in which the event took place, and in the de-

layed recall of verbal and visuospatial information.[10,21] In utero, changes in hippocampal morphology occur and the hippocampus is thought to resemble adult shape by 25 weeks of gestation. A crucial period of hippocampal development is in the first two years of life when it undergoes a growth spurt. Hippocampal volume is thought to peak between 9 years and 11 years of age, after which it resembles adult size (Figure 1).[22] Various studies have examined memory and the underlying neurobiology of memory impairments following neonatal critical illness and have shown that, just as in healthy children and adults[10,11], the hippocampus is essential for memory functioning in survivors of neonatal critical illness (please refer to the online Appendix for an overview of these studies).

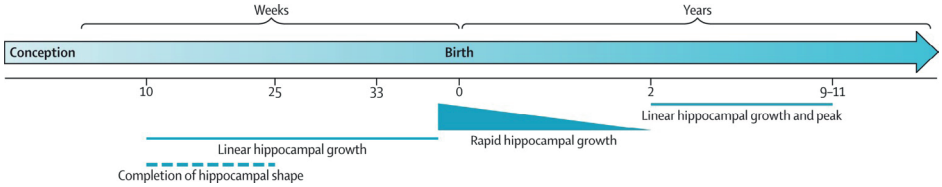

Figure 1. Schematic overview of the major phases of hippocampal development
Hippocampal morphological and positional changes occur in utero. A growth spurt occurs between the perinatal months and two years of age. Peak volume reached between 9-11 years, resembling adult size.

Preterm birth

Preterm birth is defined as birth before 36 completed weeks of gestation and accounts for 10% of all births in high-income countries.[2] Preterm birth is increasing in Europe and is the major cause of death in neonates.[2] However, survival of preterm infants is also increasing[2], and hence long-term outcomes are becoming increasingly important.

In school-age and adolescent survivors of preterm birth, impairments in speed of information processing, attention, visuospatial processing, language, executive functioning, and memory have been reported.[7] Short-term and long-term verbal and visuospatial memory deficits have been identified, even in young adults who were born preterm.[7,21,23-25] The neurobiological substrates of memory have been assessed in various developmental stages following preterm birth (online appendix). In infancy, left and right hippocampal volumes as well as shape were altered in preterm neonates compared to term-born controls at term-equivalent age.[26,27] Although hippocampal shape in infants was not related to memory function, bilateral hippocampal volume was positively associated with verbal memory at seven years of age.[23] Preterm children have consistently altered hippocampal shape and smaller left and right hippocampal volumes than do term-born controls between 7 years and 11 years of age.[19,23,28-30] Studies that have also assessed the association between the hippocampus and memory are scarce, but have shown no association between hippocampal alterations and memory impairments in school-age survivors.[19,29] This absence of association might be due to

the type of memory tests used or the involvement of other brain regions in the assessed memory functions, or both. In adolescents and young adults who were born preterm, alterations have been found in the hippocampus and surrounding brain regions, such as the hippocampal fornix and parahippocampal gyrus, have been found. In these studies, consistent associations were demonstrated between the hippocampal alterations, as well as alterations to the areas surrounding the hippocampus, that were associated with impaired memory.[24,25,31-33] One study, however, found hippocampal alterations but normal memory performance.[28] These findings might reflect brain plasticity or compensatory mechanisms, causing other brain regions to take over the function of the affected regions in the preterm brain.[21]

One study found similar hippocampal volumes in school-age children born preterm and term-born controls, despite poor memory outcome in preterm children.[34] These memory impairments may be explained by alterations in other unassessed brain areas responsible for memory functioning. However, methodological issues, such as small sample size, assessment of only one type of memory, and use of two different MRI scanners within the same cohort, might also explain these contradictory results. The severity of prematurity could also affect findings as previous studies have shown positive associations between gestational age and hippocampal volume.[35-37]

Congenital heart disease

Children with CHD who have been critically ill in the neonatal period and have had major cardiac surgery are at risk of significant neurodevelopmental problems later in life. The Boston Circulatory Trial assessed children with dextro-transposition of the great arteries (d-TGA) who underwent the arterial switch operation and found below average academic achievement, visuospatial skills, working-memory and attention at school-age and during adolescence. These impairments were found despite normal intelligence.[8,38] A meta-analysis in 5-8 year-olds who had heart surgery for CHD found similar impairments in executive functioning, attention and visuomotor integration. Furthermore, generally lower verbal memory was identified in survivors compared to healthy controls, whereas non-verbal memory was normal.[16] In CHD children tested four years after heart surgery treated with tight glucose control, worse working-memory and immediate verbal memory were found compared to healthy controls.[16] A study in children with d-TGA between the ages 8-16 years, reported specific deficits in both verbal and visual delayed memory.[39] Similar deficits have been found in adolescent survivors of CHD of differing complexity as well, even persisting into young adulthood.[20] A small number of studies have examined memory and its neurobiological correlates in survivors of CHD (online appendix). Smaller bilateral hippocampal volumes were demonstrated in 40% of school-age children who had d-TGA and cyanosis when compared to healthy controls. Hippocampal reductions were associated with worse verbal and visuospatial memory.[39]

Furthermore, 13-year-old children who had cardiopulmonary bypass surgery in infancy had smaller bilateral hippocampal volumes as well as volume loss in other parts of the limbic system's grey matter than did healthy controls.[40]

It is important to note that underlying cardiac anomaly and treatment may influence neurodevelopmental outcome. For instance, adolescents who underwent the Fontan and Norwood procedures scored below the population norm on general memory, whereas patients who underwent a different operation had normal outcomes.[15] Although assessed in a small sample size, cyanotic CHD patients had more pronounced hippocampal volume loss than acyanotic patients. Memory was not assessed.[40]

Neonatal ECMO in case of severe respiratory failure

Since the first neonatal ECMO treatment applied in 1975, nearly 40,000 neonates were treated with ECMO worldwide.[41] The annual number of neonatal ECMO runs has decreased over the years and treatment has shifted from respiratory to cardiac runs. However, 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 necessitating treatment with ECMO, mortality rates are 49%.[41] Over the past decade, standardised treatment protocols for CDH patients have reduced mortality and the need for ECMO.[42]

In school-age neonatal ECMO survivors, extensive neuropsychological assessment has shown mainly attention, verbal and visuospatial memory deficits.[17] Similar deficits were found in adolescent survivors, while other domains remained relatively unaffected.[9] Interestingly, memory deficits have also been found in children with CDH who were not treated with ECMO.[37]

Studies have examined the neurobiological substrates of long-term neuropsychological outcome following severe respiratory failure with neonatal ECMO treatment (online appendix). We found global white matter microstructure alterations and regional alterations in the limbic system in school-age neonatal ECMO survivors compared to healthy controls.[43] Specifically, hippocampal volume reductions were associated with worse delayed verbal memory in the neonatal ECMO survivors.[17] White matter microstructure alterations in the parahippocampal region of the cingulum – a white matter tract connecting the medial temporal lobe with the parietal and occipital lobes – were associated with worse visuospatial and verbal memory.[17] Similar structure-function relationships were demonstrated in CDH patients not treated with ECMO.[17] In line with these findings, in school-age survivors of acute hypoxic respiratory failure, either treated with conventional ventilator management or ECMO, smaller hippocampal volumes were identified when compared to healthy controls. These were associated with impaired memory for everyday events, and verbal and visuospatial memory deficits.[37]

HIPPOCAMPAL VULNERABILITY AND NEONATAL CRITICAL ILLNESS

The above-described findings demonstrate that memory deficits are associated with hippocampal alterations following neonatal critical illness, irrespective of underlying diagnosis. These hippocampal alterations are likely a result of both the timing and type of insults critically ill neonates are exposed to. The brain, including the hippocampus and the rest of the limbic system, develops rapidly in the third trimester and throughout the neonatal period.[44] During this period, critically ill infants are at risk of exposure to hypoxia, neuroinflammation, stress, and clinical procedures requiring general anaesthesia. The hippocampus has been found to have a selective vulnerability to these conditions associated with critical illness. The hippocampus consists of the cornu ammonis (CA) regions 1 (CA1) and 3 (CA3), the dentate gyrus (DG) and subiculum (Sub). Animal and *in vitro* models of the hippocampus have demonstrated that these subregions show differential vulnerability[11,45], which might explain why it is affected by such a wide range of conditions (Figure 2). In the next section, we will explore why the hippocampus shows a pronounced and selective vulnerability to hypoxia, neuroinflammation, stress, and anaesthetics.

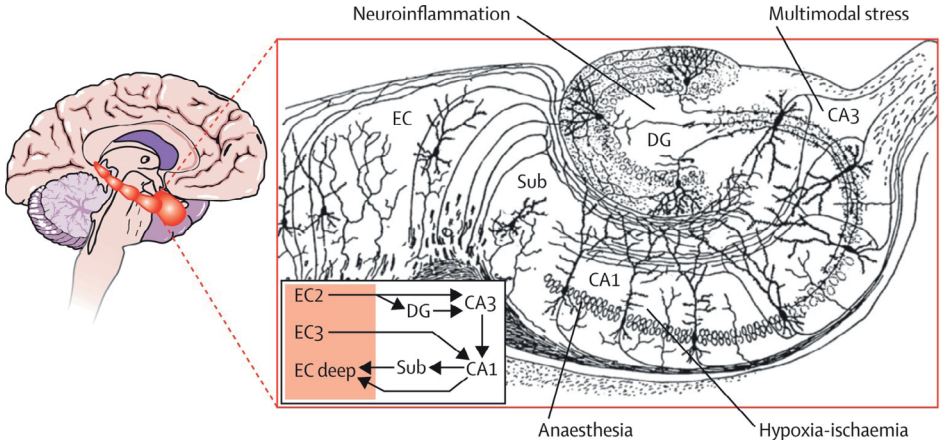

Figure 2. Vulnerability of the hippocampus to conditions associated with neonatal critical illness
Differential vulnerability of the hippocampal cornu ammonis (CA) regions 1 (CA1) and 3 (CA3), the dentate gyrus (DG) and subiculum (Sub) to hypoxic-ischaemia, neuroinflammation, stress and anaesthetics is shown.

Hypoxia

Cerebral hypoperfusion and/or hypoxemia resulting in hypoxia are common complications in preterm infants, or (near) term infants with CHD, or severe respiratory failure, either treated with or without neonatal ECMO. Studies using animal and *in vitro* models have demonstrated that the hippocampus shows more pronounced changes follow-

ing hypoxia-ischaemia than other brain structures (reviewed by Schmidt-Kastner).[47] Furthermore, differential vulnerability for hypoxia-ischaemia in the hippocampal subregions has been suggested; CA1 seems more vulnerable to acute hypoxic-ischaemia than CA3 and DG, in which relative sparing has been found. However, prolonged periods of cerebral ischaemia have been shown to damage CA3 and DG as well.[47] Differential vulnerability within the hippocampus is suggested to result from regional differences in antioxidant enzymes, inflammatory reaction and/or in the distribution of glutamatergic N-methyl-D-aspartate (NMDA) receptors.[11] This variation in vulnerability might also lead to different types of memory impairments since differential functional organisation within the hippocampal formation has been suggested as well.[44] However, this needs further study in humans.

In addition to the hippocampus, its surrounding white matter, and in particular the periventricular white matter, seems specifically susceptible to hypoxic-ischaemic insults. Using animal models, premyelinating oligodendrocytes (pre-OLs) in cerebral white matter have been identified as selectively targeted by oxidative stress. These cells account for approximately 90% of the total oligodendroglial population at 28 weeks of gestation and approximately 50% at term.[48] Increased regional susceptibility of the periventricular white matter is suggested to be due to the distribution of these pre-OLs and relative underdevelopment of distal arterial fields in these areas.[48,49] Therefore, neonates exposed to hypoxic-ischaemic injuries, even at term, might be at increased risk of myelin and axonal disruptions resulting in white matter abnormalities, which have been shown to correlate with impaired neurodevelopmental outcome.[50]

Inflammation

Critical illness is often accompanied by a marked proinflammatory response to underlying factors such as stress, infection or hypoxia-ischaemia.[51] The hippocampus has been shown to be involved in the regulation of inflammation due to its high density of microglia. Microglia in the (immature) central nervous system respond rapidly to infection or injury. In case of deleterious conditions, microglia in the hippocampus show a dynamic process of neuroprotective and pro-inflammatory responses, producing pro-inflammatory and neurotoxic factors. Using rodent models, the latter mechanism has been shown to negatively affect hippocampal neurogenesis and cellular composition in the developing brain.[52] Clinical studies in neonates have shown an elevated risk of brain injury following inflammation[51], but its specific effects on the hippocampus need further research. Behavioural effects of inflammatory damage to the hippocampus have been studied, though mostly using experimental models, demonstrating an association between pro-inflammatory cytokines in the hippocampus and memory impairments.[52]

Elevated glucocorticoid levels

Endogenous glucocorticoids

Environmental stressors from the neonatal ICU have been found to elicit physiological stress responses in critically ill infants and affect brain structure and function.[53] In response to stress, the brain's hypothalamus-pituitary-adrenal (HPA) axis is activated, causing the release of cortisol into the blood by the adrenal gland. The hippocampus is a key regulator in this system by reducing HPA axis activity following stress exposure. Cortisol binds to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), which are highly expressed in the hippocampus and excess cortisol results in hippocampal dendritic atrophy and inhibited neurogenesis.[54] Animal models have shown pronounced effects of acute stress on CA1. However, in reaction to chronic and/or multimodal stress (e.g. hours-long light, loud noise), which might be more similar to experiences in the NICU, the CA3 region showed synapse reductions, leading to poorer object recognition memory.[55] One study[54] showed that stressors in the neonatal ICU environment were associated with altered brain microstructure and functional connectivity within the temporal lobes, but not in the frontal lobe of the brain, in preterm infants (born <30 weeks). Although memory functioning was not assessed, increased stress exposure resulted in more neurobehavioral problems at term-equivalent age.[56] Stress may also be experienced by the mother during pregnancy in case of prenatally identified congenital anomalies and/or in the NICU period. Increased pre- and postnatal maternal stress has shown to affect infants' hippocampal growth in the first six months of life.[54] Maternal stress exposure is thought to have 'programming' effects on the foetal HPA axis activity. Increased maternal cortisol secretion may partly reach the foetus, increasing foetal HPA activity by reducing the number of MRs and GRs in the hippocampus.[54] Although more research in humans is needed, maternal stress may contribute to an increased risk of long-term memory impairments in critically ill neonates.[54]

Exogenous glucocorticoids

Studies in preterm born children have shown that postnatal treatment with dexamethasone – a corticosteroid used especially in preterm children to accelerate lung development – negatively affected hippocampal morhpology.[23,26] However, dexamethasone might not affect children treated with neonatal ECMO and CHD as much, as corticosteroids are generally used less frequently in these patients.[43]

Anaesthetics

Possible negative effects on the developing brain of prolonged, general anaesthesia has recently resulted in an FDA warning regarding its use in children younger than three years.[57] Although clinical studies in humans are scarce and findings are mostly based on experimental studies, hippocampal development may be affected by the use of com-

monly used anaesthetic agents, resulting in long-term memory deficits. Commonly used anaesthetics bind either to γ-aminobutyric acid (GABA) or NMDA receptors. The GABA and NDMA receptor systems are crucial for neuronal connection and communication in the developing brain, and if unavailable lead to neuroapoptosis.[57] Various types of anaesthesia, such as midazolam, propofol and ketamine, have been suggested to disrupt memory formation through its effects on the hippocampus.[58] Memory formation and recall are dependent on a system of persistent strengthening of synapses following high levels of stimulation, called Long-Term Potentiation (LTP). LTP, which mainly happens in the hippocampus, relies heavily on NMDA. In a rat model, midazolam was found to affect pyramidal neurons in the CA1 region and memory by suppression of LTP.[59] However, translating findings from animal models to the developing human brain is restricted[60] and research in humans and/or specific disease models is crucial. In very preterm neonates (24-32 weeks of gestation), high exposure to midazolam was negatively associated with hippocampal growth from birth to term-equivalent age, adjusted for clinical confounders including gestational age, days of mechanical ventilation, and number of surgeries.[61] However, memory outcome was not assessed. In school-age children who underwent general anaesthesia before one years of age, significantly worse memory recall was found compared to untreated controls, whereas IQ remained unaffected.[57] The association between memory deficits and altered hippocampal morphology was not assessed.

A COMMON NEURODEVELOPMENTAL PATHWAY FOLLOWING NEONATAL CRITICAL ILLNESS

In this Review we present evidence to suggest a shared vulnerability of the hippocampus that is associated with long-term memory impairments across critically ill neonates. On the basis of this evidence, we speculate that a final common neurodevelopmental pathway exists following neonatal critical illness (Figure 3). It is important to note that the patient groups described in this review have varying brain development trajectories due to variations in illness onset (e.g. congenital anomaly developing in utero versus postnatal sepsis necessitating neonatal ECMO), gender, and gestational age. These factors are likely to interact with the exposure to harmful conditions associated with neonatal critical illness, and may influence how and when the hippocampus is affected. The exact pathophysiological mechanisms of the hippocampal alterations in each of these patient groups remains unknown and needs further research.

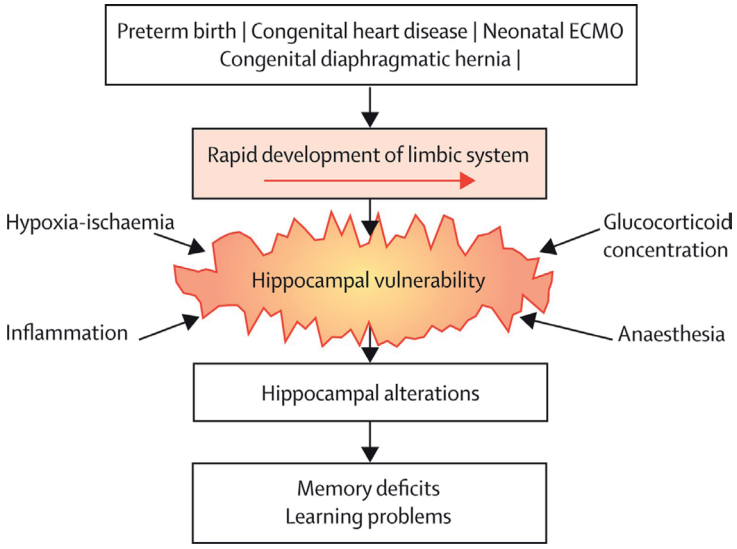

Figure 3. A common neurdevelopmental pathway following neonatal critical illness
Neonatal critical illness survivors share an increased risk of hippocampal alterations due to vulnerability to common conditions associated with neonatal critical illness, leading to long-term memory deficits**.**

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

In the previous sections, the shared memory impairments and the role of the hippocampus across critically ill infants was highlighted. In this section, we describe how the findings outlined in this review guide the direction of future research and contribute to the realisation of early identification of patients at risk as well as the development of targeted intervention or treatment modalities.

Early risk prediction

Currently, the identification of patients at risk of school problems relies solely on neuropsychological assessment. However, evaluating higher-order cognitive functions such as memory cannot be reliably conducted until school-age.[7] The identification of patients at risk of academic problems is as such often too late. The neuropsychological deficits, that may have remained unidentified or unspecified, may by then have already led to school problems. Neuropsychological assessment should therefore be primarily used as a diagnostic tool, rather than as a prediction tool. Patients at risk should be identified before academic difficulties are present. In order to do so, early predictors of long-term memory impairments, favourably measurable in infancy, are needed.

Firstly, hippocampal volume alterations, if detected in infancy, could potentially serve as such a predictor of impaired long-term memory. MRI is a non-invasive neuroimaging technique and therefore a useful tool to assess the hippocampus in infants. Findings

in preterm infants have shown that MRI can be reliably performed without sedation and that infant hippocampal volumes, measured at term-equivalent age, correlate with memory outcomes both at two years and seven years of age.[23,27] Future studies are needed to find cut-off points to separate normal from abnormal hippocampal volume in infancy using a healthy control group. Furthermore, differences in the timing and type of hippocampal injury are likely to exist across critically ill infants because of differences in brain development associated with disease aetiologies. For instance, brain alterations have been found as early as in the third trimester in CHD patients[5] and the immature preterm brain may respond differently than the term brain to the strenuous conditions associated with neonatal critical illness.[49] Longitudinal studies are therefore imperative to accurately delineate the longitudinal hippocampal growth trajectories across these patient groups. Also, given the rapid hippocampal growth during the first two years of life[22], longitudinal studies will help to determine the best time to assess hippocampal morphology as an early predictor of memory.

Up to this point, the hippocampus has been primarily quantified through volumetry using structural MRI. This method has been shown to be very robust and useful to accurately parcellate hippocampal volume. In future studies, it would be interesting to focus on details in the hippocampal parcellation by obtaining finer resolution images and multi-contrast imaging, or using alternative modalities such as diffusion imaging. This may contribute to a better understanding of the differential vulnerability of the hippocampal subregions, and, if combined with neuropsychological assessment, its suggested differential involvement in various memory processes.[11,45] However, importantly, MRI does not provide information on the exact anatomical or molecular mechanisms underlying the hippocampal alterations. The specific contribution of the risk factors outlined in this review to the hippocampal alterations and long-term memory deficits therefore remains speculative.

Secondly, hypoxia is consistently shown to affect hippocampal morphology. The severity of cerebral hypoperfusion sustained in the perinatal period may therefore be another risk factor of long-term memory problems following neonatal critical illness. Adequate ways to monitor cerebral metabolism, haemodynamics and autoregulation in the NICU are urgently needed since current methods, such as transcranial Doppler ultrasonography or near-infrared spectroscopy, do not have enough resolution for targeting the brain region of interest in this context.

Treatment opportunities

Although the hippocampus is a highly vulnerable brain structure, it has also been shown to exhibit more plasticity and capability of long-term neurogenesis than other brain structures.[11] This makes it a promising target for intervention strategies to improve long-term memory following neonatal critical illness.

Neuroprotection

Another group of critically ill neonates at high risk of hypoxic-ischaemic injuries are survivors of perinatal asphyxia. In contrast to the patient groups described in this review, in a significant number of neonates with perinatal asphyxia overt, chronic neurological abnormalities are present as well as long-term severe morbidities such as cerebral palsy and intellectual disability.[62] Whole body therapeutic hypothermia is the standard of care in full-term neonates with perinatal asphyxia and has shown to improve neurologic outcomes.[63] Using animal and *in vitro* models, mild to moderate therapeutic hypothermia has been shown to reduce hippocampal cell death following an hypoxic or ischaemic insult.[64] However, while patients with perinatal asphyxia experience an acute phase of hypoxia[65], more prolonged exposure to hypoxia may exist in the patient groups described in this review. Furthermore, hypothermia likely does not protect the hippocampus against the other types of harmful conditions associated with critical illness. Future randomized controlled trials are needed to assess if and to what extent therapeutic hypothermia affects the hippocampus and memory in these groups before it can be recommended as a routine neuroprotective strategy.

Stress prevention

As demonstrated, stress may negatively affect the hippocampus and memory.[54] Reducing stress exposure during NICU stay could therefore be beneficial for critically ill infants as well as relatively feasible in clinical practice. Indeed, decreasing light and sound in the NICU, as well as encouraging physical parent-infant contact during hospital stay, have been shown to positively affect development.[66] Future studies assessing whether such stress reduction measures specifically influence hippocampal development and memory improvements in neonatal critical illness survivors are needed.

Cognitive interventions

Studies evaluating 'brain training' or computerized cognitive training programs have increased over the last decade. However, its effectiveness remains controversial. Cognitive training programs are based on the idea that repetitive mental exercise of one cognitive task will result in improved functioning that may generalize to other tasks with a similar underlying system. A widely evaluated cognitive training for both children and adults is Cogmed working-memory training.[67] Studies have fairly consistently shown improvements in the trained verbal and visuospatial working-memory skills, but less consistently in untrained functions such as delayed memory recall.[68] Working-memory, the main targeted function of Cogmed, relies primarily on frontal-parietal networks.[67] It is unclear how, or if, Cogmed influences the plastic nature of the hippocampus. Neuroimaging studies assessing the exact effects of Cogmed on hippocampal function and different types of memory are needed in survivors of neonatal critical illness. Cur-

rently, randomized controlled trials are being performed with school-age survivors of neonatal ECMO (Trial Registration Number: NTR4571) and children and adolescents with CHD (Clinical Trial Numbers: NCT03023644 and NCT02759263). Other types of cognitive training programs used specifically for memory rehabilitation may be effective but need further research in neonatal critical illness survivors.[69]

An important part of effectively using cognitive intervention is the identification of neonatal critical illness survivors that have significant memory deficits, and are thus in need of treatment. While early identification of these patients is ideal, in today's practice, identifying children with such deficits remains reliant on neuropsychological assessment at school-age. It is therefore crucial to conduct neuropsychological assessment in which, in addition to intelligence, specific neuropsychological outcomes are the primary focus following neonatal critical illness.

Exercise interventions

Exercise might enhance memory and learning by targeting the hippocampus. Greater aerobic fitness has been associated with hippocampal volume as well as improvements in memory in children.[70] Whether improvements persist in the long-term remains largely unknown and needs further study in survivors of neonatal critical illness.

CONCLUSION

With this review, we propose a common neurodevelopmental pathway following neonatal critical illness by demonstrating that survivors of preterm birth, CHD, and severe respiratory failure share an increased risk of long-term memory deficits and related hippocampal alterations. Rather than being a consequence of underlying diagnosis, we suggest the shared vulnerability to be related to common complications or conditions associated with neonatal critical illness. These include hypoxia, neuroinflammation, stress, anaesthetics, or a complex interplay of these factors at different postconceptional ages. Our findings underline the need of broadening our focus from prevention of mortality to long-term outcome of critically ill infants. Follow-up should incorporate standardized assessment of specific neuropsychological functions, such as memory, at school-age. Early identification of patients at risk may be feasible using infant hippocampal volumes assessed with non-invasive structural MRI. Future prospective studies on memory rehabilitation with the use of cognitive or exercise training are needed in neonatal critical illness survivors. Lastly, increased awareness of the vulnerability of the hippocampus and memory deficits following neonatal critical illness is crucial to prepare survivors for future academic problems and participation in society.

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