The prognostic value of MRI-TEA in long-term outcomes of extreme prematurity - a scoping review

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Abstract

Background- Survival of infants born EP (<32 weeks GA) is increasing due to advances in obstetrical practices and clinical management at the NICU. However, those infants still have long-term effects containing neurodevelopmental motor- and sensory impairments, and specific cognitive-, behavioural-, social- and emotional outcomes.
Aims- This scoping review aims to appoint the paucities of current MRI studies and their correlations with neurodevelopmental outcomes. We also aim to discuss the relevance of 7T MRI and its capability in infant EP prognosis.
Methods and procedures- A PubMed database screening has been performed. Studies have been removed based on our exclusion criteria by screening the title and abstracts first. After this, the remaining full text articles were again screened on the exclusion criteria. Lastly, articles were manually added after a manual search to provide background information on premature-related brain injuries and prognostic biomarkers of MRI on long-term outcomes.
Outcomes and results- we identified 23 peer-reviewed articles, most (n= 17) were published between 2019 and 2022. A wide variety of variables like MRI sequences, MRI scoring systems, neurodevelopmental tests and the age of test administer were found. A general conclusion of the outcomes and the MRI prognostic biomarkers is provided, highlighting the paucities of 1.5T- and 3T MRI studies and the advantages of 7T MRI.
Conclusion and implications- 1.5T- and 3T MRI studies predict motor- and severe cognitive outcome, however those studies lack in subtle or moderate findings, other neurodevelopmental outcomes or metabolic- and pathophysiological findings. 7T MRI would be relevant because spatial and spectral resolution increases, while the acquisition time remains the same. 7T MRI-TEA techniques as T2WI, SWI, PC-MRA, ihMT and MRS could reveal more prognostic biomarkers associated with long-term outcomes.
Key words: extremely premature, white matter injury, 7 Tesla, longitudinal, neurodevelopmental impairments, prognostic biomarkers

What this paper adds?

- *Extreme premature-related brain injuries*
- *An overview of prognostic MRI studies focusing on long term effects of extreme prematurity*
- *The biomarkers of 1.5T- and 3T MRI scans on extreme prematurity*
- *The prognostic role of 7T MRI in long-term effects of extreme prematurity*

Introduction

Survival of infants born extremely preterm (EP), infants born <32 weeks gestational age (GA), is increasing due to advances in obstetrical practices and clinical management at the neonatal intensive care unit (NICU) (Vesoulis & Mathur, 2017). However, those infants often have long-term effects containing neurodevelopmental impairments like motor-, sensory-, cognitive-, behavioural-, social and emotional outcomes (Johnson & Marlow, 2017). Those outcomes exceed up to 50% of infants born EP (Marlow et al., 2005; Volpe, 2009). Focusing on the prognosis of magnetic resonance imaging (MRI), up to 20% did not had significant qualitative abnormalities on 3T MRI images at term age (TEA) (Back, 2017).

During the early postnatal weeks, white matter development starts at the subventricular zone (SVZ) of the lateral ventricles, which contains multipotent neural stem cells. Gliogenesis is the process by which those stem cells differentiate in new astrocytes and oligodendrocytes. Besides, a rapid growth of blood vessels additionally occur which supplies the SVZ. After gliogenesis, cells migrate and proliferate towards overlying structures including neocortex. Precursors of the glial cells, pre-myelinating oligodendrocyte progenitors (Pre-OL), are in high densities presented in the white matter (Vesoulis & Mathur, 2017). Myelination is another important developmental process which differentiate the pre-OLs into mature myelinating OLs, which causes a developmental resistance to hypoxia-ischemia and oxidative stress (Back, 2017; Semple et al., 2013). Furthermore, during white matter development other processes like elaboration of dendrites and establishment of synapses occur, called synaptogenesis (Volpe, 2019). This all creates coordination between glial, vascular, and synaptic growth to ensure interactions are instituted (Semple et al., 2013).

Third-trimester brain development is characterized by critical and energy-dependent biological processes needed to support optimal brain growth (Semple et al., 2013). Infants born EP are more vulnerable to neurological damage because the environment of the infant, NICU incubator, lacks in womb-containing protective factors. The most typical neurological damage is white matter injury (WMI) (Vesoulis & Mathur, 2017). Pre-OLs are playing a significant role in the premature brain, they account for 90% of the peak period of WMI in infants born preterm (Vesoulis & Mathur, 2017). Furthermore, three risk factors could also lead to oxidative stress from hypoxic-ischemic injury (HIE). Those risk factors are heart-rate disturbances, immature vascular supply, and disturbances in vascular autoregulation (Vesoulis & Mathur, 2017). The initial response to WMI is proliferation deficiency characterized by a significant increase in pre-OLs in subacute lesions. This results in expansion of pre-OLs which generate new pre-OLs to replace those that degenerate during acute WMI (Back, 2017). The second process is a disruption in myelination of the pre-OLs into mature OLs. In this matter, hypomyelination is another hallmark of the disease (Back & Rosenberg, 2014). The consequences of pre-OLs injury leads to axonal deficiency and diminish cortical grey matter (cGM) and thalamic/basal ganglia (deep grey matter (dGM)) volumes because of retrograde and anterograde effects (Volpe, 2009, 2019).

As part of the neuro-inflammatory responses, microglia (other glial brain cells) can be destructive to cells like pre-OLs. Microglia generate free radicals, secrete injurious cytokines, and enhances excitotoxicity (Volpe, 2019). Expression of glutamate is inducing maturation-dependent death of pre-OLs by non-receptor and receptor-mediated mechanisms (Khwaja & Volpe, 2008). Intrinsic vulnerability of pre-OLs to oxidate stress and cell death occur due to the non-receptor mediated mechanism involving glutamate competition of cysteine and depletion of intracellular glutathione (Khwaja & Volpe, 2008; Vesoulis & Mathur, 2017). The extrinsic vulnerability of pre-OLs is caused by the glutamate receptor-mediated mechanism of microglia causing cell death (Khwaja & Volpe, 2008; Vesoulis & Mathur, 2017). The critical point is that the premature brain is overloaded with microglia, all reacting after a variety of clinical factors like postnatal infections, hypoxia-ischemia, hypoxemia, hypocarbia, metabolic acidosis and hypoglycaemia (Back, 2017; Blüml et al., 2013). Besides, astrocytes (macro glial brain cells) , can also become reactive and exhibit a variety of metabolic changes that are deleterious to other white matter components like pre-OLs (Volpe, 2019). Three types of cell death occur named focal cystic necrosis, focal microscopic and diffuse non-necrotic lesions (Vesoulis & Mathur, 2017). Periventricular leukomalacia (PVL) is a form of WMI characterized by this

process, and which occurs mostly at the ventricular wall. Cystic necrosis occurs within hours and leads to death of all cellular elements (glia, axons, blood vessels and neural progenitors) because of severe energy failure. Diffuse chronic WMI is the process that leads to focal necrosis and is non-reversible (Back, 2017).

Technological advancements like MRI provide insight into the neurological damage of infants born EP (Vesoulis & Mathur, 2017). The water density of an infant's brain is higher (92-95%) than the adult brain (82-85%) (Arthur, 2006). In addition, because the infant's brain is a smaller region of interest compared to the adult brain, reduction of signal-to-noise ratio occurs when using adult MRI protocols. For these reasons, it is important to create specific MRI protocols, with different sequences, for the neonatal brain during TEA. Specific MRI protocols have been created and been applied on 1.5T MRI scanners. However, in 2004, the first 3T MRI scan study focusing on infants born preterm has been reported (Annink et al., 2020; Rutherford et al., 2004). Increase use of 3T MRI in clinical research appear to happen since then, because it acquires images with shorter acquisition time and greater anatomical resolution due to the increased signal-to-noise ratio (Lawrence & Inder, 2008). Even though MRI is the criterion standards to assess brain injuries in infants, prognosis remains difficult because of the 1) shortage in detailed high-resolution neuroimaging, 2) careful correlations of neuropsychological outcomes and 3) co-morbidities (Annink et al., 2020; Volpe, 2009).

The shortage in detailed high-resolution neuroimaging becomes known when comparing it with pathophysiological techniques. Diffuse chronic WMI lesions are observed with MRI in less than 5% of infants in NICU facilities (Volpe, 2019). Most of the focal necrosis observed post-mortem, are less than 1 mm in size which could not be detected with current MRI scanners and protocols (Volpe, 2019). Ultra-high magnetic field imaging, like 7T MRI, could improve prognosis, however it might also coexist with health-risk issues. This scoping review aims to appoint the paucities of current MRI prognostic studies and their correlations with neurodevelopmental outcomes of infants born EP. Furthermore, we aim to discuss the relevance of 7T MRI and its capability in infant EP prognosis. A layman's summary about this paper is provided in appendix A.

Material and methods

Search methods

A search with PubMed was carried out in October 2022. Figure 1 summarizes the complete literature search and screening procedure. We defined three core categories of interest (COIs) for the search process to follow our aims: MRI techniques, long-term brain effects and prematurity. Search terms used in the advanced search toolbox of PubMed are presented in table 1. We narrowed our search into title and abstract. The search resulted in a total of 1239 relevant records. In the following step, we screened these 1239 records.

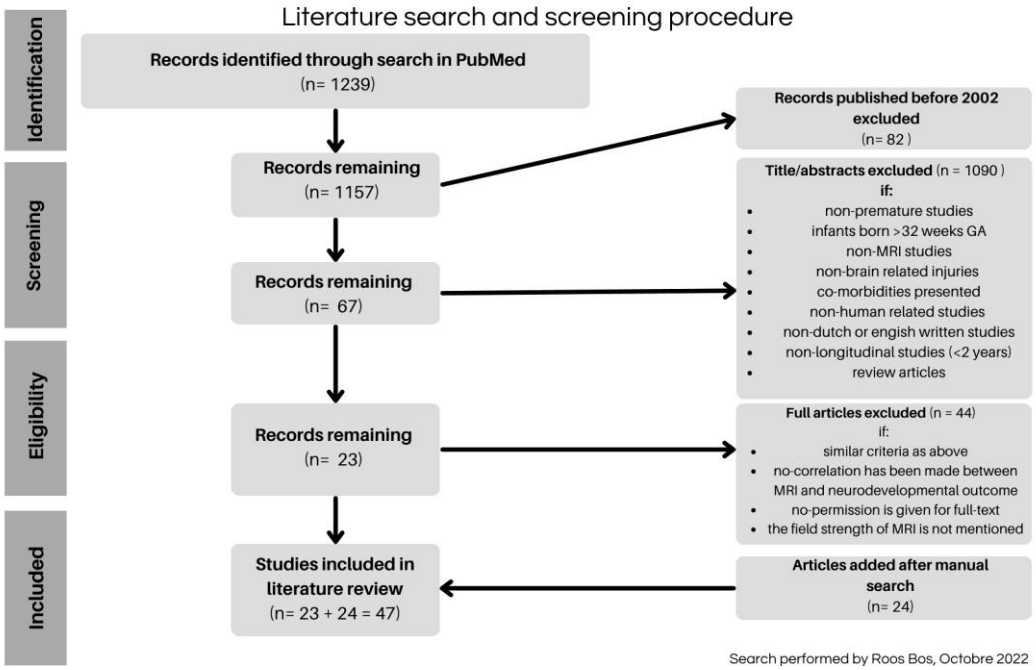

Figure 1. Literature search and screening procedure

Screening

Articles published before 2002 were excluded to focus on significant advancement during the last 20 years. Second, by screening the title and abstracts, we removed studies of non-prematures; infants born >32 weeks GA; non-MRI studies; non-brain related injuries; co-morbidities; non-human related; non-Dutch or English written; non-longitudinal correlations (<2 years) and review articles. Third, by screening the full-text of the remaining studies, articles were again excluded on basis of the similar title/abstract criteria (n= 35); if no-permission is given to full-text articles (n= 1); if the prospective value of MRI is not calculated for neurodevelopmental outcome (n= 7); or if the field strength of MRI is not mentioned (n= 1). Lastly, articles were manually added after a search to provide background information on premature-related brain injuries and different MRI protocols and their prognostic biomarkers on long-term outcomes (n= 24).

Table 1
Search categories and terms

Categories	***Search terms***
MRI techniques	*7T* OR 7-Tesla OR MRS OR CEST OR SWI OR PC-MRI OR 3-Tesla OR 3T* OR MRI*
Long-term brain effects	*"Brain injur*" OR "Brain damage" OR "cerebral injur*" OR "cerebral damage" OR "cerebral def*" OR "cerebral impairment*" OR "brain def*" OR "brain impairment*" OR "neurodevelopmental dis*"*
Prematurity	*prem* OR preterm OR neonat* OR infant**

Note. All terms were used in an advanced PubMed search on Title/Abstract

Results

According to our search and screening procedure, we identified forty-seven peer-reviewed articles. Twenty-three articles are longitudinal studies focusing on the neurodevelopment prognostic biomarkers of MRI by infants born EP. A detailed overview of those longitudinal prospective studies is given (Table 2; Appendix B). Ten studies used 1.5T MRI scans, ten studies used 3T MRI scans, and three studies used 1.5T and 3T. The sample size (SS) of infants EP is on average 112 [21- 239]. Nine studies included infants born extremely preterm (EP), so before 28 weeks GA, while the others also included the infants born very preterm (VP) which is between 28-32 weeks GA. Most studies did measure the neurodevelopmental outcome at 24 or 30 months (CA). One study performed neurodevelopmental outcome measurements around 312 months (13 years).

Longitudinal assessments

The Bayley Scales of Infant Development (BSID) and Bayley Scales of Infant and Toddler Development (BSITD) tests were used mostly to assess the neurodevelopmental outcomes of infants born EP. This test focuses on five different domains: Cognitive-, language-, motor-, social-emotional- and adaptive functions. BSID contains additionally a mental developmental index (MDI) and a psychomotor development index (PDI). Other used longitudinal assessments are described in Appendix C.

MRI-TEA protocol for the neonatal brain

Multiple MRI sequences were used to detect brain abnormalities at TEA in infants born EP. In this subsection the eight different sequences are discussed.

1. **The T1-weighted (T1-W) spin-echo (SE) and T2-weighted (T2-W) fast/turbo spin-echo (FSE/TSE)** are the commonly used sequences for detecting anatomical disturbances in the neonatal period (Arthur, 2006; Lawrence & Inder, 2008). T1-W images have a hyperintense signal of the cGM compared to the hypointense signal of the WM. Therefore, this sequence can illustrate the differentiation between WM and GM in the neonatal brain. This differentiation can be easily observed around 26 weeks GA but occur to be isointense during TEA. Processes like maturation but also cortical folding of the neonatal brain can therefore be detected with T1-W images (Arthur, 2006). Besides, acute WMI first appear to be hypointense on T1-W images, which becomes hyperintense after the acute phase (Lawrence & Inder, 2008). On the other hand, myelination leads to T2 shortening, therefore T2-W images could detect myelination as a hypointense signal. Zones of migrating glial cells can be shown as low-intensity symmetrical bands on T2-W images at the periventricular zone (Arthur, 2006). Acute WMI appear to be hyperintense on T2-W images. After the acute phase it becomes hypointense on T2-W images (Lawrence & Inder, 2008).

   Other derivatives of the T1-W sequence are 3D T1-W and/or Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE/3D SPGR). Which is a turbo-FLASH technique with magnetization prepared inversion pulses (George et al., n.d.). Although MRPRANGE is volumetric, T1-W SE and MPRANGE sequences look similar. The only noticeable difference is that MPRANGE sequences have better contrast between GM and WM. FLASH is a sequence of fast field echo (FFE), which is useful to acquire fast scans in uncooperative patients. CSF is dark on the FLASH images (George et al., n.d.). Instead of SE or FSE/TSE, two studies made slightly adjustments in the protocol like double echo (DE) and gradient echo (GE).

2. **Proton density (PD**) measures with a longer repetition time but has also a short echo time like T1 images. Therefore, it measures the tissue with the highest concentration of hydrogen atoms (George et al., n.d.). This tissue will produce the strongest signal so becomes the brightest on the image.

3. **Diffusion weighted MRI (DWI)** is another important sequence which measures the self-diffusion of water through the brain tissue (Lawrence & Inder, 2008). The quantity of tissue diffusivity is apparent diffusion coefficient (ADC). The values of ADC can be decreased due to HIE in the neonatal brain. HIE leads to cell death and cellular swelling, resulting in increased tortuosity of extracellular pathways (Allen D. Elster, 1994). However, DWI remains challenging because restriction of ADC in the certain areas can only be interpreted during the acute phase (Arthur, 2006; Lawrence & Inder, 2008).

4. **Diffusion Tension imaging (DTI)** measures relative anisotropy (RA) or fractional anisotropy (FA). Anisotropy decreases during the first week of severe and moderate WMI, while ADC decreases only with severe injury. This is because anisotropy is more detailed and has information about the direction of diffusion, while ADC only detects the severity (Allen D. Elster, 1994). Pairing FA and ADC can add information on severity and timing of injury (Lawrence & Inder, 2008).

5. **MR spectroscopy (MRS)** can analyse the chemical composition of tissues in voxels. It detects small metabolites existing in millimolar (mM) concentrations (Allen D. Elster, 1994). These metabolites can be detected because, due to their chemical environment, they resonate differently at slightly different frequences. The chemical shift is the expression of two molecular species separated by frequencies. The most common applied nucleus is the 1H proton. It can detect metabolite levels of for example N-acetyl aspartate (NAA), glutamine (Gln), lactate (Lac) and glutamate (Glu). NAA (free amino acid) is present in excessive amounts in the neuronal tissue and developing OLs, which makes it an indicator of intact central nervous tissue. Gln and Gln are important to detect the neuro-inflammatory response of microglia to induce cell death, already discussed in the introduction. Another example, H-MRS detects lactate which is a useful marker of tissue injury because of hypoxia. The metabolite lactate is the product of the energy metabolism in a poor-oxygen environment causing HIE (Lawrence & Inder, 2008; Wisnowski et al., 2013).

6. **Magnetic resonance angiography and magnetic resonance venography (MRA/MRV)** are techniques to delineate arterial and venous supply and topography (Lawrence & Inder, 2008). Hemodynamics, blood flow or oxygen measurements, establish this topography (Dubois et al., 2021). Phase-contrast MRA (PC-MRA) last less than a minute to measure volume flow in cm/s.

7. **Susceptibility-weighted imaging (SWI) and GRE/T2*** are sequences sensitive to haemoglobin breakdown products. Infants born before 32 weeks GA are vulnerable to develop intraventricular or intraparenchymal haemorrhages as consequences of HIE. (Cabaj et al., 2012)

8. **Magnetization Transfer MRI (MTR)** calculates the ratio between free water and water bound to macromolecules such as proteins and lipids. MTR studies has limitations in the neonatal brain due to acquisition time and energy deposition. This technique can detect myelin-associated macromolecules, but also macromolecular density of axonal cytoskeleton components such as microtubules and neurofilaments. Inhomogeneous Magnetization Transfer (ihMT) is focused on the myelin-rich structures. (Dubois et al., 2021)

Scoring system of MRI sequences

A frequently used scoring system is the qualitative structural analysis of Inder et al. (2003). It scores the images on the presence and severity of WMI. It is graded into five different scales: the nature and extent of WMI, periventricular WM volume loss, the presence of any cystic

abnormalities, ventricular dilatation and thinning of the corpus callosum (Woodward et al., 2005). Further in time, Kidokoro et al. (2013) came with a novel scoring system (Haebich et al., 2020). It is an overall rating of WM-, cGM-, dGM-, cerebellum-, and global brain abnormality. The WM abnormality scale ranges from 0 to 17 which is a sum of six subscales assessing the presence and severity of: cystic lesions, signal abnormalities, myelination delay, thinning of the corpus callosum, lateral ventricle dilation and volume reduction. CGM abnormality (0-9) is the sum of three subscales: signal abnormality, delayed gyral maturation and increased extracerebral space. DGM and cerebellum abnormality (both 0-7) comprise two subscales assessing signal abnormality and volume reduction. The global brain abnormality scale (0-40) is the sum of CWM, CGM, DGM and the cerebellum scale. Higher scores reflect higher severity. Other scoring systems are described in more detail in Appendix D.

Strength of the MRI field

If we compare the 1.5T and 3T longitudinal studies of table 2, is it difficult to precisely frame the prognostic biomarkers of MRI-TEA on long-term effects of prematurity. This is because the variables like MRI sequences, MRI scoring systems, neurodevelopmental tests and the age of test administer do all vary. However, a general conclusion of the outcomes and the MRI prognostic biomarkers can be formulated. Table 2 shows that 1.5T studies found associations between moderate-severe WMI and motor impairments like cerebral palsy (n= 4), moderate-severe WMI and severe cognitive delay (n= 1), dGM and severe cognitive delay (n= 1), moderate-severe WMI/cGM/dGM and severe cognitive delay (n= 1), ventricular dilation and low motor scores (n= 1). There were also studies which did not find any association (n= 3). Most studies, especially the newest 1.5T study of Sheng et al., showed that motor impairments are the most predictable. This is because specific locations like posterior limb of the internal capsule (PLIC) induce motor onset, while for instance cognitive functions establish through collaboration of multiple brain regions. However, 1.5T studies lack in identifying predictors of subtle or milder cognitive impairments and in finding metabolic- or pathophysiological associations. The 3T studies are more diverse in MRI scores which has ensured prognostic findings in language- and visual impairments (WM reduction, basal ganglia, and thalamus abnormalities). Multiple studies showed that WM reduction, ventricular volume, cortical thickness and dGM all have influence on IQ scores later-on. Furthermore, same as in 1.5T, multiple predictors of motor and severe cognitive outcomes have been found. For example, cerebellar abnormalities predict cognitive impairments, while a higher volume in the hippocampal area improves motor outcomes. WMI predicts fine motor outcomes, while WMI and dGM both affect gross motor outcomes. A normal range in MRI metrics on brain growth, like biparietal width (BPW), predict as well a normal psychomotor as a normal cognitive outcome. However, similar as the 1.5T studies, more prognostic biomarkers in other neurodevelopmental outcomes like language-, socio-emotional- and adaptive functions need to be found. Same as metabolic- or pathophysiological associations.

With ultra-high field MRI, like 7T, it becomes easier to detect detailed abnormalities compared to the studies earlier performed with lower fields. This has been proven already in focal brain lesions in adult epileptic- and multiple sclerosis patients (de Ciantis et al., 2016; Harrison et al., 2015). It improves spatial resolution while the acquisition time remains the same, leading to extreme anatomical details particularly with SWI or T2* contrast. Structures with slightly different magnetic proportions, introducing detectable field variation at ultra-high fields, are mostly tissues with a high iron content, densely distributed myelinated axons and veins, where the deoxyhaemoglobin level is high (Trattnig et al., 2018). Therefore, so far in adults, SWI improvement enables diagnosis of microbleeds and visualization of microvasculature but is also well suited for studying deep nuclei characterized by high iron content (Annink et al., 2020; Cho et al., 2011). In infants born EP, PC-MRA becomes also more relevant. This method in 3T MRI did lack on spatial information, therefore PC-MRA had to be segmented by anatomical brain images to calculate the perfusion value (Dubois et al., 2021). Due to the spatial improvement of 7T MRI, ihMT could also become less limited in the neonatal brain. This technique has been rare in studies because the acquisition time was not optimal for infants born EP. However, it is quite relevant because it could detect the

myelinization, which is a hallmark of WMI. MRS also improves due to spectral resolution, which improves accuracy and represents a far larger number of detectable brain metabolites (Trattnig et al., 2018). More precise MRS could gain information about the Gln and Glu peaks. For instance, NAA, which is presented in excessive amounts in the neuronal tissue and developing OLs, creates a high peak in MRS. However, Glu and Gln do both have a smaller peak and are closely related so are not easy to distinguish at the 3T MRS technique. 7T MRS would make it easier to make a distinction between both metabolites. It is important to make a distinction because a measurement between healthy or the severity of illness can be measured. The healthy circumstance is the re-uptake of Glu, whereby it first is converted into the non-toxic Gln (Wisnowski et al., 2013). As already described in the introduction, otherwise a high amount of extracellular Glu is presented inducing excitotoxicity.

Thus, to gain knowledge in the total picture of brain deficits in infants born EP, it is important to find MRI abnormalities in all different organization levels. Annink et al. showed that 7T MRI obtained good-quality imaging for T2WI, SWI, MRA and MRV and MRS in infants born EP (Annink et al., 2020). Therefore, future studies should use 7T imaging to detect abnormalities in:

- Anatomical images of WM or GM contrast, ventricular dilatation, and cortical thinning on T2WI
- Iron content of dGM nuclei, microbleeds and microvasculature with SWI
- Blood flow with for instance PC-MRA
- Myelin-associated macromolecules, but also to the macromolecular density of axonal cytoskeleton components such as microtubules and neurofilaments with ihMT
- Metabolic changes in for instance Glu and Gln with MRS

Discussion

Our scoping review provides overall interesting opportunities for future 7T MRI studies, to predict long-term outcomes in infants born EP. The prognostic paucities of 1.5T- and 3T MRI could be diminished with 7T MRI because of the spatial and spectral improvement while the acquisition time remains the same. Therefore, metabolic- or pathophysiological prognostic biomarkers, but as well biomarkers of other neurodevelopmental impairments might be detected. However, MRI in an infants born EP is still challenging because the illness ranges from mild-, to moderate- and severe impairments, but as well sedation complications, susceptibility to motion and the limited experience by the MR technologist (Lawrence & Inder, 2008). Ultra-high magnetic field MRI, with adult protocols, would bring more health-risk issues to infants. Small adaptations to the material and protocols are enough to create a feasible and safe detection in infants (Annink et al., 2020; Burkett et al., 2021). Dedicated coils with optimizes size in relation to the size of the head, makes it possible to maximize the signal-to-noise ratio even further (Dubois et al., 2021). Annink et al. showed in a virtual infant with a standard head coil, that specific absorption rate (SAR) levels at 7T are comparable to SAR levels in an adult model (Annink et al., 2020; Malik et al., 2021). The largest concern was the increasing risk of body temperature because of the higher local and global SAR levels. The global SAR and the peak local SAR of the virtual infant model did not exceed the SAR of the adult model, which means the head coil makes it a feasible method.

The main limitation of the current study is that it suffered from limited time. The paper had to be performed in only five weeks where inclusion and exclusion criteria had to be determined, 1239 articles on title/abstract had to be screened, and sixty-seven articles on full text, analyse twenty-three articles on different parameters and finally I had to write the entire paper. For this reason, only a PubMed search has been performed and arbitrary exclusion criteria has been chosen. According to the inclusion and exclusion criteria, longitudinal studies before 2 years were excluded, because we decide to set boundaries between long-term- and short-term outcomes. To diminish the complexity of all correlations, we decided to also exclude co-morbidities. Several studies did also focus on electroencephalogram (EEG) and MRI, whereby the MRI element is used as a golden standard. We decided to also exclude this because the focus has not been on MRI and therefore only correlations between EEG-MRI and EEG-long-term outcome has been performed. Besides, we decided to only include English and Dutch written articles. This comes with a risk of bias but circumvented between this or a misinterpretation of the content. Above this, all longitudinal studies with infants before 32 weeks were included. Due to the neonatal survival of infants born before 28 weeks GA, the term for infants born preterm is changed. Earlier, infants born before 32 weeks GA were called EP. However, another subdivision of the period 28-32 weeks GA has occurred. Nowadays, infants before 28 weeks GA are called EP and infants born between 28-32 weeks GA are called very preterm (VP). To still compare all the earlier studies, we have chosen to include all infants before 32 weeks GA, and define them as EP.

We also made a selective choice in discussing 7T techniques. Multiple 7T techniques are available, like for instance ASL instead of PC-MRA. However, there has been chosen to focus only on the techniques which would be optimal for infants born EP. In this example this would be PC-MRI because it has a faster time acquisition (Dubois et al., 2021).

According to the future, deep learning algorithms could make diagnosis/prognosis easier and more accurate. A combination of fMRI and deep learning can be used to detect brain region impairments in the infants born EP on a larger scale (Dubois et al., 2021). In addition, a connectome study can reveal different impaired brain hubs which might predict for instance long-term socio-emotional impairments (the socio-emotional functions work due to a collaboration of multiple brain regions). Even as brain regions can collaborate, different organization levels could also collaborate within the brain. For this matter, it would be remarkably interesting to compare CSF- and blood sampling with EEG and MRI. All this information combined, might give a better prognosis. Furthermore, co-morbidities makes the prognosis more challenging. However, understanding the neurodevelopmental impairments of infants born EP, may provide researchers with vital links to autism, congenital heart disease and other diseases. Finally, another important future direction will be to map the evolution of

WMI over months to years to clearly identify the contributions of disrupted myelination and axonal dysfunction in infants born EP. It is especially important to define the window of opportunity for interventions and to repair the WMI. In 1.5T- and 3T MRI this was not achievable because it could not discriminate disrupted myelination from other pathological processes, however 7T MRI might make this distinction.

Conclusion

This scoping review provides an overview of the current longitudinal studies of infants born EP. It gives insight on prognostic biomarkers of 1.5T- and 3T MRI-TEA and neurodevelopmental outcomes above 2 years of age. Most studies showed prognostic biomarkers of motor- and severe cognitive outcome, however they lack in subtle or moderate findings, or other neurodevelopmental outcomes like language-, socio-emotional- and adaptive functions. Besides, the prognostic biomarkers also lack in metabolic or pathophysiological organization levels. In future studies, 7T MRI would be relevant because spatial and spectral resolution increases, while the acquisition time remains the same. 7T MRI-TEA techniques as T2WI, SWI, PC-MRA, ihMT and MRS could reveal more prognostic biomarkers associated with long-term outcomes.

Acknowledgements

The author would like to thank Evita Wiegers for her supervision during the five weeks.

References

Allen D. Elster. (1994). *MRIquestions.com*.

Annink, K. v., van der Aa, N. E., Dudink, J., Alderliesten, T., Groenendaal, F., Lequin, M., Jansen, F. E., Rhebergen, K. S., Luijten, P., Hendrikse, J., Hoogduin, H. J. M., Huijing, E. R., Versteeg, E., Visser, F., Raaijmakers, A. J. E., Wiegers, E. C., Klomp, D. W. J., Wijnen, J. P., & Benders, M. J. N. L. (2020). Introduction of Ultra-High-Field MR Imaging in Infants: Preparations and Feasibility. *American Journal of Neuroradiology*, *41*(8), 1532–1537. https://doi.org/10.3174/ajnr.A6702

Arthur, R. (2006). Magnetic resonance imaging in preterm infants. *Pediatric Radiology*, *36*(7), 593–607. https://doi.org/10.1007/s00247-006-0154-x

Back, S. A. (2017). White matter injury in the preterm infant: pathology and mechanisms. In *Acta Neuropathologica* (Vol. 134, Issue 3, pp. 331–349). Springer Verlag. https://doi.org/10.1007/s00401-017-1718-6

Back, S. A., & Rosenberg, P. A. (2014). Pathophysiology of glia in perinatal white matter injury. In *GLIA* (Vol. 62, Issue 11, pp. 1790–1815). John Wiley and Sons Inc. https://doi.org/10.1002/glia.22658

Blüml, S., Wisnowski, J. L., Nelson, M. D., Paquette, L., Gilles, F. H., Kinney, H. C., & Panigrahy, A. (2013). Metabolic maturation of the human brain from birth through adolescence: insights from in vivo magnetic resonance spectroscopy. *Cerebral Cortex (New York, N.Y. : 1991)*, *23*(12), 2944–2955. https://doi.org/10.1093/cercor/bhs283

Burkett, B. J., Fagan, A. J., Felmlee, J. P., Black, D. F., Lane, J. I., Port, J. D., Rydberg, C. H., & Welker, K. M. (2021). Clinical 7-T MRI for neuroradiology: strengths, weaknesses, and ongoing challenges. *Neuroradiology*, *63*, 167–177. https://doi.org/10.1007/s00234-020-02629-z/Published

Cabaj, A., Bekiesińska-Figatowska, M., & Mądzik, J. (n.d.). *MRI patterns of hypoxic-ischemic brain injury in preterm and full-term infants-classical and less common MR findings*. http://www.polradiol.com/fulltxt.php?ICID=883379

Cho, Z. H., Oh, S. H., Kim, J. M., Park, S. Y., Kwon, D. H., Jeong, H. J., Kim, Y. B., Chi, J. G., Park, C. W., Huston, J., Lee, K. H., & Jeon, B. S. (2011). Direct visualization of Parkinson's disease by in vivo human brain imaging using 7.0T magnetic resonance imaging. *Movement Disorders*, *26*(4), 713–718. https://doi.org/10.1002/mds.23465

de Ciantis, A., Barba, C., Tassi, L., Cosottini, M., Tosetti, M., Costagli, M., Bramerio, M., Bartolini, E., Biagi, L., Cossu, M., Pelliccia, V., Symms, M. R., & Guerrini, R. (2016). 7T MRI in focal epilepsy with unrevealing conventional field strength imaging. *Epilepsia*, *57*(3), 445–454. https://doi.org/10.1111/epi.13313

Dubois, J., Alison, M., Counsell, S. J., Hertz-Pannier, L., Hüppi, P. S., & Benders, M. J. N. L. (2021). MRI of the Neonatal Brain: A Review of Methodological Challenges and Neuroscientific Advances. In *Journal of Magnetic Resonance Imaging* (Vol. 53, Issue 5, pp. 1318–1343). John Wiley and Sons Inc. https://doi.org/10.1002/jmri.27192

George, R., dela Cruz, J., Singh, R., & Dr. Rajapandian Ilangovan. (n.d.). *Mrimaster.com*.

Haebich, K. M., Willmott, C., Scratch, S. E., Pascoe, L., Lee, K. J., Spencer-Smith, M. M., Cheong, J. L. Y., Inder, T. E., Doyle, L. W., Thompson, D. K., & Anderson, P. J. (2020). Neonatal brain abnormalities and brain volumes associated with goal setting outcomes

in very preterm 13-year-olds. *Brain Imaging and Behavior*, *14*(4), 1062–1073. https://doi.org/10.1007/s11682-019-00039-1

Harrison, D. M., Oh, J., Roy, S., Wood, E. T., Whetstone, A., Seigo, M. A., Jones, C. K., Pham, D., van Zijl, P., Reich, D. S., & Calabresi, P. A. (2015). Thalamic lesions in multiple sclerosis by 7T MRI: Clinical implications and relationship to cortical pathology. *Multiple Sclerosis*, *21*(9), 1139–1150. https://doi.org/10.1177/1352458514558134

Johnson, S., & Marlow, N. (2017). Early and long-term outcome of infants born extremely preterm. In *Archives of Disease in Childhood* (Vol. 102, Issue 1, pp. 97–102). BMJ Publishing Group. https://doi.org/10.1136/archdischild-2015-309581

Khwaja, O., & Volpe, J. J. (2008). Pathogenesis of cerebral white matter injury of prematurity. In *Archives of Disease in Childhood: Fetal and Neonatal Edition* (Vol. 93, Issue 2). https://doi.org/10.1136/adc.2006.108837

Lawrence, R. K., & Inder, T. E. (2008). Anatomic Changes and Imaging in Assessing Brain Injury in the Term Infant. In *Clinics in Perinatology* (Vol. 35, Issue 4, pp. 679–693). https://doi.org/10.1016/j.clp.2008.07.013

Malik, S. J., Hand, J. W., Satnarine, R., Price, A. N., & Hajnal, J. v. (2021). Specific absorption rate and temperature in neonate models resulting from exposure to a 7T head coil. *Magnetic Resonance in Medicine*, *86*(3), 1299–1313. https://doi.org/10.1002/mrm.28784

Marlow, N., Wolke, D., Bracewell, M. A., & Samara, M. (2005). Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth. In *n engl j med* (Vol. 352). www.nejm.org

Rutherford, M., Malamateniou, C., Zeka, J., & Counsell, S. (2004). MR imaging of the neonatal brain at 3 Tesla. *European Journal of Paediatric Neurology*, *8*(6), 281–289. https://doi.org/10.1016/j.ejpn.2004.08.003

Semple, B. D., Blomgren, K., Gimlin, K., Ferriero, D. M., & Noble-Haeusslein, L. J. (2013). Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. In *Progress in Neurobiology* (Vols. 106–107, pp. 1–16). https://doi.org/10.1016/j.pneurobio.2013.04.001

Trattnig, S., Springer, E., Bogner, W., Hangel, G., Strasser, B., Dymerska, B., Cardoso, P. L., & Robinson, S. D. (2018). Key clinical benefits of neuroimaging at 7 T. *NeuroImage*, *168*, 477–489. https://doi.org/10.1016/j.neuroimage.2016.11.031

Vesoulis, Z. A., & Mathur, A. M. (2017). Cerebral autoregulation, brain injury, and the transitioning premature infant. In *Frontiers in Pediatrics* (Vol. 5). Frontiers Media S.A. https://doi.org/10.3389/fped.2017.00064

Volpe, J. J. (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. In *The Lancet Neurology* (Vol. 8, Issue 1, pp. 110–124). https://doi.org/10.1016/S1474-4422(08)70294-1

Volpe, J. J. (2019). Dysmaturation of Premature Brain: Importance, Cellular Mechanisms, and Potential Interventions. In *Pediatric Neurology* (Vol. 95, pp. 42–66). Elsevier Inc. https://doi.org/10.1016/j.pediatrneurol.2019.02.016

Wisnowski, J. L., Blüml, S., Paquette, L., Zelinski, E., Nelson, M. D., Painter, M. J., Damasio, H., Gilles, F., & Panigrahy, A. (2013). Altered Glutamatergic Metabolism Associated with

Punctate White Matter Lesions in Preterm Infants. *PLoS ONE*, *8*(2). https://doi.org/10.1371/journal.pone.0056880

Woodward, L. J., Edgin, J. O., Thompson, D., & Inder, T. E. (2005). Object working memory deficits predicted by early brain injury and development in the preterm infant. *Brain*, *128*(11), 2578–2587. https://doi.org/10.1093/brain/awh618