Diffusion tensor imaging in neonatal encephalopathy: a systematic review

Megan Dibble,1,2 Mary Isabel O’Dea,3 Tim Hurley, Angela Byrne, Gabrielle Colleran, Eleanor J Molloy, Arun Lawrence Warren Bokde

ABSTRACT

Background and objective Diffusion tensor imaging (DTI) during the first few days of life can be used to assess brain injury in neonates with neonatal encephalopathy (NE) for outcome prediction. The goal of this review was to identify specific white matter tracts of interest that can be quantified by DTI as being altered in neonates with this condition, and to investigate its potential prognostic ability.

Methods Searches of Medline and the Cochrane Database of Systematic Reviews were conducted to identify studies with diffusion data collected in term-born neonates with NE.

Results 19 studies were included which described restricted diffusion in encephalopathic neonates as compared with healthy controls, with the posterior limb of the internal capsule and the genu and splenium of the corpus callosum identified as particular regions of interest. Restricted diffusion was related to adverse outcomes in the studies that conducted a follow-up of these infants.

Conclusions Obtaining diffusion measures in these key white matter tracts early in life before pseudonormalisation can occur can not only identify the extent of the damage but also can be used to examine the effectiveness of treatment and to predict neurodevelopmental outcome.

BACKGROUND AND OBJECTIVE

Neonatal encephalopathy (NE) is a heterogeneous clinical syndrome of disordered neurological function in the term-born neonate. It is characterised by ‘subnormal level of consciousness or seizures, and often accompanied by difficulty with initiating and maintaining respiration and depression of tone and reflexes’ (D’Alton, p896).1 Afflicting approximately two to six in every 1000 live births,2 NE is one of the leading causes of infant morbidity and mortality in late preterm and term neonates. The behavioural, motor and cognitive consequences of NE are generally associated with the severity of the brain injury, and can vary significantly between cases of mild, moderate and severe NE. Severity of NE is most frequently graded using the Sarnat staging.3 Moderate–severe NE is associated with adverse outcomes (long-term morbidity and mortality) at a rate of approximately 30%. Survivors of NE are at risk of several long-term neurodevelopmental impairments, which may include cerebral palsy, intellectual disability, impairment of language skills or working memory, and problem behaviour.4 Previously, it was thought that there were minimal sequelae for neonates with mild NE; however, recent studies suggest that mild NE is also associated with abnormal MRI findings and abnormal neurodevelopmental outcome.3,5

NE can arise due to a variety of adverse perinatal issues, such as hypoxia-ischaemia, metabolic infectious and genetic disorders. As such, the term NE does not refer to any one specific aetiology. The term hypoxic-ischaemic encephalopathy (HIE) has often been used in the literature to describe cases in which NE was apparently caused by perinatal asphyxia.4 NE is now the preferred term of use as it takes into account the multifactorial aetiology, and will be used for this review—which will focus on the predictive value of DTI in NE due to perinatal asphyxia—however, studies describing the condition as HIE have also been taken into account.

MRI is a widely used tool in the assessment of NE, providing information about the nature, location, timing and severity of the injury, and guiding clinical decision-making. Several standardised scoring

What is already known on this topic?

► T1-weighted and T2-weighted MRI imaging shows basal ganglia/thalamus and watershed cortical injury in neonatal encephalopathy (NE), but may underestimate damage in the first week of life.

► Diffusion-weighted imaging (DWI), however, can show abnormalities in the first few days of life—the critical period where decisions are to be made regarding treatment.

► DWI has been shown to be an effective predictor of neurodevelopmental outcome in NE.

What this study adds?

► White matter tracts that consistently show altered diffusion in NE are the posterior limb of the internal capsule and genu and splenium of the corpus callosum.

► Lower fractional anisotropy values in these regions are associated with poorer scores on neurodevelopmental clinical assessments at follow-up.

► This data may be used to assess the impact of therapeutic hypothermia on the injury, and as a prognostic tool to predict possible outcomes.
Review

systems have been developed for the assessment of NE. The most widely known and used is the Barkovich scoring system,\(^6\) in which T1-weighted and T2-weighted images are assessed to grade the damage to the brain in NE infant in terms of basal ganglia/thalamus injury, and watershed cortical injury. Recent MRI scoring systems, such as that of Weeke and colleagues,\(^7\) now also include diffusion-weighted imaging (DWI) as part of their assessment, which has been shown to be an effective predictor of outcome in NE.\(^8\) DWI examines the integrity of white matter in the brain by utilising the anisotropy of water diffusion, and the three-dimensional shape of this diffusion is analysed through diffusion tensor imaging (DTI). DWI/DTI has an advantage over conventional MRI, which may underestimate diffusion abnormalities can be seen within the first few hours of life and extend further over the next few days, and so infants can be scanned early, in the critical period where decisions are to be made regarding treatment, and in certain situations redirection of care. At present, the only intervention for infants with NE is therapeutic hypothermia, a neuroprotective intervention that needs to be started within 6 hours of birth to have proven benefit, with a number needed to treat of seven to eight to improve one infant’s outcome.\(^10\)

The purpose of this review was to examine current DTI findings in NE infants, to determine which regions of white matter are most commonly affected, and how this type of injury may relate to neurodevelopmental outcome.

METHODS

A systematic review of the literature was performed using the guidelines from the Meta-analysis of Observational Studies in Epidemiology\(^11\) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.\(^12\) Medline (PubMed) and the Cochrane Database of Systematic Reviews were searched using combinations of the terms (neonatal encephalopathy), (hypoxic ischaemic encephalopathy) and (diffusion tensor imaging). References of included studies were also examined, and duplicates were eliminated. Figure 1 shows the literature search and selection process using the PRISMA flowchart.

Studies were included based on the following inclusion criteria: (1) neonates with clinically diagnosed neonatal HIE or NE, (2) neonates born near or at term (35 gestational weeks or above) and (3) diffusion-weighted images were obtained along with the conventional MRI. Studies were excluded if there was insufficient detail/information, the neonate was born prematurely (<35 weeks gestation), neonates were scanned after 1 month of life, animal models were used or if grey matter alone was studied. The review included studies with infants with mild, moderate or severe NE, and that were either untreated or treated with therapeutic hypothermia. Studies were also assessed for quality and bias with the application of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement\(^13\) to selected articles.

Data extracted from the studies included population characteristics, imaging protocols, definition of NE, the results of any conventional MRI findings or scoring criteria, diffusion metrics for the white matter and any recorded outcome assessments. The above variables were then compiled into a summarising table (see table 1).

We aimed to define and quantify the specific white matter tracts, or regions of interest (ROIs), that seem to be implicated in NE. Using the JHU-ICBM DTI-81 white matter labels\(^14\) as a starting point, we calculated the number of times each of these ROIs was mentioned in the results section of these studies as having altered diffusion measures. We then visualised the results by creating a greyscale image using FSLeyes (http://www.fmrib.ox.ac.uk/fsl). Using FSL's FMRIB58 fractional anisotropy (FA) image as a template, we placed the JHU-ICBM DTI-81 white matter labels atlas as an overlay, selecting the relevant tracts and removing the tracts that were not part of the results in the literature review. The relative weighting of the tracts were a function of the number of times it appeared in the literature review.

RESULTS

In all, 19 studies were included in our final list for review, which included DTI data from 557 NE infants and 112 healthy controls.\(^15\)–\(^33\) These studies all met the guidelines outlined in the STROBE statement\(^13\) in regard to quality and bias. Follow-up/outcomes were available in 11 of these studies.\(^17\)–\(^19\) 23–\(^25\) 28–\(^30\)–\(^32\) On the whole, these studies described decreased levels of FA in NE infants compared with healthy controls, with the severity of decreases in FA being associated with the severity of the NE and, when applicable, the severity of outcomes. One study also showed significantly lower FA in non-cooled neonates than neonates treated with therapeutic hypothermia.\(^15\) We calculated the frequency of ROIs, the results of which are shown in table 2. Three key ROIs were identified—the posterior limb of the internal capsule (PLIC), and the genu and splenium of the corpus callosum (CC). As we included studies that used a whole brain approach as well as an ROI approach, we also noted the number of times a significant change in global white matter was found. These frequencies were then converted to a greyscale image, in which the tracts with the most mentions (PLIC, CCGenu, CCSplen), are shown as the brightest (white), and the tracts with the least mentions are shown as the darkest (black), with various levels of grey in between (figure 2).

![Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search and selection process.](http://fn.bmj.com/Arch Dis Child Fetal Neonatal Ed: first published as 10.1136/archdischild-2019-318025 on 10 December 2019. Downloaded from by copyright.)
Table 1 Data extracted from the literature for the main variables of interest

<table>
<thead>
<tr>
<th>Authors</th>
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<tr>
<td>Porter et al&lt;sup&gt;5&lt;/sup&gt;</td>
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<td></td>
<td>1–21 days</td>
<td>101/108</td>
<td>FA</td>
<td>–</td>
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<td>Whole brain—TBSS</td>
<td>Compared with the control group FA was significantly reduced not only in several white matter tracts in the non-cooled infants but also in the internal capsule in the cooled group</td>
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<td>Non-cooled infants had significantly lower FA than the cooled treated infants, indicating more extensive damage, in the anterior and posterior limbs of the internal capsule, the CC, and optic radiations</td>
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<td>Lally et al&lt;sup&gt;6&lt;/sup&gt;</td>
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<td>2–10 days</td>
<td>12/11</td>
<td>FA</td>
<td>–</td>
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<td>Whole brain—TBSS</td>
<td>17 had HIE and healthy term</td>
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<td>Within 3 weeks</td>
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<td>FA values from manual ROI and TBSS were strongly correlated. Both methods found decreased FA in 7 ROIs for HIE infants—left and right periventricular regions, splenium, genu, left and right CSTs, left temporal tract, and right temporal tract</td>
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<td>Tusor et al&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Withing 3 weeks</td>
<td>43</td>
<td>FA</td>
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<td>Abnormalities were frequently observed in white matter (n = 40, 91%) and cortex (n = 31, 70%) while only 19 (27%) had abnormal basal ganglia/thalami</td>
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<td>Those infants with moderate to severe encephalopathy had globally reduced FA compared with the rest of the cohort</td>
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<td>Reduced white matter FA was associated with Sarnat stage, deep grey matter injury and MR spectroscopy N-acetylaspartate/ choline, but not Thompson scores</td>
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<td>Of the surviving babies, 45% had adverse neurodevelopmental outcomes</td>
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<td>Seo et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Appar score less than 5 at birth</td>
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<td>36–44 weeks</td>
<td>27/35</td>
<td>FA, AD, RD</td>
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<td>18 normal GA, AD, RD</td>
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<td>or continued need for</td>
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<td>Six had an abnormal tone, motor problems or developmental delay (GMFCS level III–IV) and two were GMDS–R (DQ) scores below the mean; motor, communication and academic difficulties</td>
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<td>resuscitation within 10 min</td>
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<td>of moderate, 100% of severe)</td>
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<td>of birth OR acidosis within</td>
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<td>These lower values of OFA were seen in several regions of the brain, including the right centrum semiovale, lateral thalamus and genu of the CC, anterior limb of the internal capsule, PLIC, external capsules, and ventricles</td>
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<td>60 min after birth</td>
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<td>Two had watershed with normal FA, and two had watershed with abnormal FA</td>
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<td>Moderate- to-severe</td>
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<td>The GMDS–R showed a significant linear correlation between FA values and developmental quotient (DQ) and all its component subscale scores</td>
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<td>encephalopathy (lethargy,</td>
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<td>One or more of hypotonia,</td>
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<td>Reduced white matter FA was associated with Sarnat stage, deep grey matter injury and MR spectroscopy N-acetylaspartate/choline, but not Thompson scores</td>
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<td>abnormal reflexes, absent/weak suck, clinical seizures</td>
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<td>Abnormal EEG background</td>
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<td>Significantly lower FA values were seen in all three groups (n = 40, 91%) and cortex (n = 31, 70%) while only 19 (27%) had abnormal basal ganglia/thalami</td>
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<td>for at least 30 min</td>
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*FA = fractional anisotropy, GA = gestational age, HIE = hypoxic ischemic encephalopathy, IFO = inferior frontal orbital, ILF = inferior longitudinal fasciculus, PLIC = posterior limb of internal capsule, RD = radial diffusivity, SE = slice thickness, TBSS = tract-based spatial statistics, WFA = whole brain analysis, WM = white matter.*
### Table 1 Continued

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<tr>
<td>Gao et al.</td>
<td>Evidence of fetal distress (heartbeat abnormalities or meconium-stained amniotic fluid) or neonatal distress (umbilical cord pH less than 7.2 and/or Apgar score less than 7 within 1 min of birth)</td>
<td>Mild HIE and healthy term</td>
<td>Within 28 days</td>
<td>24/17</td>
<td>FA, J, J’ 2, 3, 3</td>
<td>Mild HE injuries were presented as punctate WM injury with hypointensity in T2WIs and hyperintensity in T1WIs and watershed WM injury with hypointensity in T2WIs and hyperintensity in T1WIs</td>
<td>Whole brain—TBSS</td>
<td>► We found decreased FA in CP, PLIC and CR in all injured neonates; Decreased FA and increased J, J’ in CST, CCgenu, IC and CCsplen in mild HIE neonates; Regions with FA decreases were accompanied by increased J, J’ and λ1, which contributes to axial diffusivity and reflects the number and diameter of axons, without obvious changes; These findings suggested that such mild HIE within minutes injury mainly led to deficits or delays in myelination, instead of damage on axons</td>
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<td>Kline-Fath et al.</td>
<td>Metabolic acidosis (pH less than 7.1 and/or base deficit less than 10); Agar score of 5 or less within 5 min of birth</td>
<td>HE with seizures and HE without seizures</td>
<td>Within 2 weeks</td>
<td>25/23</td>
<td>FA</td>
<td>MRI scans were graded for injury in watershed areas, BGT and PLIC</td>
<td>▶ The seizure group had significantly more injury within white matter, basal ganglia, posterior limb of internal capsule and watershed areas compared with the group without seizures; The severity of injury in all measured areas increased with increasing seizure severity; The seizure group also had lower FA values in PLIC and the optimium of CC</td>
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<td>Carrasco et al.</td>
<td>Diagnosis of moderate to severe HE</td>
<td>Cooled HE</td>
<td>Within 10 days</td>
<td>25</td>
<td>MO</td>
<td>MIN scoring system. (0): normal. (1A): minimal cerebral lesions only, without BGT/PLIC/ALIC/watershed. (1B): more extensive cerebral lesions, without BGT/PLIC/ALIC/watershed. (2A): BGT/PLIC/ALIC/watershed abnormalities without cerebral lesions. (2B): BGT/PLIC/ALIC/watershed abnormalities with cerebral lesions. (3): Cerebral hemispheric devastation</td>
<td>ROB: CCgenu, CCsplen, PLIC, ALC</td>
<td>Neurons with blood pressure measurement within optimal MAP during rewarming had less brain injury by NRBN score; Longer duration of MAP within optimal MAP during hypothermia correlated with higher mean diffusivity in the anterior centrum semiovale and pons; Blood pressure deviation below optimal MAP was associated with lower mean diffusivity in cerebral and white matter; Higher optimal MAP values related to lower mean diffusivity in the basal ganglia, the thalamus, the PLIC, the posterior centrum semiovale and the cerebellar white matter</td>
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<td>Li et al.</td>
<td>Diagnosis and inclusion criteria were in accordance with HE diagnostic criteria and clinical classification of practical neonatal HE</td>
<td>Moderate HE and severe HE and healthy term</td>
<td>10–14 days</td>
<td>14/8/0</td>
<td>ADC, IA</td>
<td>▶ NBNA at 15 days (behavioural ability, active and passive muscle tension, primitive reflexes and evaluation of general condition) — scores significantly different among the three groups, lowest scores in severe HE and correlation coefficient highest for the PLIC</td>
<td>ROB: 20 including the PLIC, ALC, bilateral parietal cortex, deep WM of frontal lobe, CCgenu, CCsplen, head of caudate nucleus, thalamus, thalamic, paras</td>
<td>FA values in the PLICs and in the thalamus showed statistically significant differences between the moderate and severe groups, and were significantly different between the control and moderate groups; White voxels in the PLICs, PLICs and ALCs showed statistically significant differences between the moderate and severe HIE groups; The fiber numbers in the PLICs, cingulate gyrus, SLFs and IFOFs were significantly different between the moderate and severe HIE groups; NBNA scores were significantly different among the three groups, with the severe HE group having the lowest scores</td>
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**Lemmon et al**<sup>6</sup>  
[ ► pH of 7.0 or less or base deficit of 16 or more within 1 hour of birth  
► Acute intrapartum event  
► Apgar score of 5 or less within 10 min of birth or assisted ventilation at birth for at least 10 min  
► Required hypothermia without discontinuation between 72 hours  
► Neonatal encephalopathy  
► Clinical encephalopathy (Sarnat 1–2)  
► Other known perinatal events  
► Clinical perinatal events (e.g., Apgar score ≤5 at 1 min of birth, pH ≤7.4, or any other significant event) |

**Cooled HIE and healthy term**  
1–28 days  
57/12  
FA, MD  
Barkovich scoring (1) normal (2) mild injury of periventricular WM (3) hyperintense signal or restricted diffusion (4) moderate injury of BGT or cortex (5) severe injury of BGT and cortex  
RO: bilateral thalamic, supratentorial, middle, and inferior CPs, and the dentate nuclei  
FA values of the thalamus and MD values of the superior cerebellar peduncle were significantly lower in patients with evidence of moderate or severe injury on MRI than in controls |

**Leon et al**<sup>7</sup>  
[ ► Apgar score ≤5 at 1 min of birth or required repositioning at birth |

**Cooled HIE**  
7–10 days  
45  
FA, MD, A2 RD  
Barkovich scoring B-S and WS  
Miller scoring for WM mild, moderate, severe  
NNNS:  motor performance  
► Significant associations were observed between DTI corticospinal tract integrity and NNNS neuromotor performance in HIE newborns. Neonatal neuromotor performance was also related to later early childhood motor outcomes |

**Massaro et al**<sup>6</sup>  
[ ► Birth weight ≤1800 g or greater  
► Metabolic acidosis and/or low Apgar score  
► Signs of moderate-to-severe clinical encephalopathy |

**Cooled HIE**  
7–10 days  
50  
FA, MD, A2 RD  
Barkovich scoring B-S and WS  
Miller scoring for WM mild, moderate, severe  
RO: CSTs in the CP, PLIC, CS, CC  
Lower CC and CST F A were associated with lower MDX and PDI, respectively  
MD showed significantly decreased values in many regions of white and grey matter, and difusivity showed the best predictive value in the genu of CC, and radial diffusivity was significantly decreased in fronto parietal WM  
The decrement of FA showed the best AUC in the PWWM |

**Ancora et al**<sup>2</sup>  
[ ► Moderate or severe HIE (Sarnat) |

**Cooled HIE**  
4–16 days  
15  
FA, MD, A1, A2  
Barkovich scoring B-S and WS  
Miller scoring for WM mild, moderate, severe  
RO: supratentorial regional, posterior central, occipital, and bilateral WM  
Functional and metabolic profiles of cerebral palsy, pathological plaques, and WM injury in children with severe HIE were significantly related to the PWWM |

**Gano et al**<sup>20</sup>  
[ ► Clinically recognizable encephalopathy  
► One or more of severe distress at delivery, requirement for resuscitation at birth, Apgar score ≤5 at 5 min and metabolic acidosis (umbilical artery pH <7.1) in newborns |

**HE**  
3 days  
19  
FA, MD  
Barkovich scoring normal, WS, BN, focal and multifocal 
Therapeutic hypothermia associated with an attenuated reduction of MD in GM and WM from days 1 to 3  
Hypothyroidism was also associated with increased neuronal metabolism and WM integrity as well as reduced oxidative metabolism |

**Wendy et al**<sup>21</sup>  
[ ► Abnormal low patterns  
► Feeding difficulties  
► Abnormal tone |

**HE and healthy term**  
Within 3 weeks  
207  
ADC, BA, RA  
BGT grading normal mild (lesions small and focal with normal myelination in the PLIC), moderate (lesions multifocal with equivocal or abnormal PLIC or severe/complete BGT abnormality with abnormal PLIC)  
WM also graded normal, moderate or severe  
BA: BGT, lateral ventricle, thalamic, periventricular WM, choroid plexus, thalamic nuclei, thalamus, thalamus, and hypothalamus  
During the first week, RA values were decreased with both severe and moderate BGT and WI injury, whereas ADC values were reduced only in severe WM injury and some severe BGT injury |

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<td>van Pul et al</td>
<td>Clinical symptoms of NE present in first 3 days of life with two or more of fetal heart rate rate abnormalities, umbilical artery pHi less than 7.10, meconium stained fluid, Agar score after 5min of less than 7</td>
<td>HE</td>
<td>Within 10 days</td>
<td>22</td>
<td>ADC, FA, AD</td>
<td>- 11 neonates had focal white matter injury</td>
<td>Follow-up MRI at 13 m</td>
<td>ROI: CC and WM</td>
<td>- Changes in lesions were characterised by a large decrease (40%) in all eigenvalues, with a stronger decrease in the direction perpendicular to the fibres, resulting in increased anisotropy index</td>
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<tr>
<td>Al Amrani et al</td>
<td>Born at 36 weeks GA or after</td>
<td>Cooled HIE</td>
<td>10 days</td>
<td>29</td>
<td>ADC, FA</td>
<td>Barkholt's scoring: 0 for no brain injury, 1 for focal ganglia injury pattern, 2 for watershed injury pattern and 3 to 4 for near-total injury pattern</td>
<td>Adverse outcomes: cerebral palsy, global developmental delay, epilepsy</td>
<td>ROIs: thalamus, PLIC, lentiform nucleus, front and posterior WM, cortical GM</td>
<td>Among those newborns developing adverse outcomes, ADC values were significantly decreased on days 2–3 of life and increased around day 30 of life in the thalamus, PLIC and the lentiform nucleus</td>
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<td></td>
<td>Evidence of fetal distress, for example, history of antepartum event, cord pH ≤7.0, base deficit ≤16, or continued need for ventilation initiated in birth for at least 10 min</td>
<td>Moderate or severe HIE</td>
<td></td>
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<tr>
<td>Kansagra et al</td>
<td>Born at 36 weeks GA or after</td>
<td>Newborn NE and 6 months NE</td>
<td>0 months and 6 months (excluded from this review)</td>
<td>12</td>
<td>FA, NOS, FW (NODD)</td>
<td>–</td>
<td>Infants assessed with a validated neonate score: 0 for normal development, 1 for abnormal tone or reflexes, 2 for abnormal tone and reflexes, 3 for functional deficit of severe, 4 for cranial nerve involvement with motor abnormality and 5 for specific quadriplegia</td>
<td>ROIs: PLIC, AUC, OR, CG genu, CC genu</td>
<td>At birth, the CC collectively demonstrated significantly higher FA than the AUC or OR</td>
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<td></td>
<td>Evidence of fetal distress, for example, history of antepartum event, cord pH ≤7.0, base deficit ≤16, or continued need for ventilation initiated in birth for at least 10 min</td>
<td>Moderate or severe HIE</td>
<td></td>
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<tr>
<td>Law et al</td>
<td>Retrospective diagnosis of NE, all cooled</td>
<td>NE (normal MRI) and NE (abnormal MRI) and healthy preterm at term equivalent</td>
<td>5–18 days</td>
<td>122/412</td>
<td>ADC, IA</td>
<td>–</td>
<td>ROIs: PULC, temporal occipital, parietal and frontal WM, CG genu, CC genu</td>
<td>We found significant reductions in measure of FA in white matter in the ANE neonates compared with the control group</td>
<td></td>
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</tbody>
</table>

- ADC, apparent diffusion coefficient; AUC, anterior limb of the internal capsule; ANE, encephalopathic neonate with an abnormal MRI; BGT, basal ganglia trauma; BPD, Bronchopulmonary Dystrophy; CDSS, Conners' Developmental Scales; CST, corticospinal tract; DWI, diffusion weighted imaging; DWI, diffusion weighted imaging; FA, fractional anisotropy; FV, free water fraction; GMFS, Gesell’s Developmental Scales; HIE, hypoxic-ischaemic encephalopathy; IOG, infant of a gestational age (weeks) × intrauterine weight (g); IP, intrauterine pressure; IUGR, intrauterine growth restriction; JIPDA, Jaundice in Premature Infant Development Assessment; KID, Neurodevelopmental Scales; MD, mean diffusivity; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; NNE, near-normal neonates; PULC, parieto-occipital uncal; PRO, posterior limb of the internal capsule; S1, superior longitudinal fasciculus; SLI, social-communication impairment; SP, superior parietal lobe; ST, superior temporal cortex; SUIT, structural imaging update tool; T2, T2-weighted; T2*; T2-star; T2* weighted; T1, T1-weighted; T1 Hypo, T1 hypointense; T1 iso, T1 isointense; T1 hyper, T1 hyperintense; T2 hyp, T2 hypointense; T2 iso, T2 isointense; T2 hyper, T2 hyperintense; T2* hyp, T2* hypointense; T2* iso, T2* isointense; T2* hyper, T2* hyperintense; U1, U1 wave; U2, U2 wave; U3, U3 wave; WM, white matter; Y, years.
Table 2  A summarising table of ROIs implicated in NE from the literature and how often they were mentioned (ROIs chosen based on the JHU-ICBM DTI-81 white matter atlas)

<table>
<thead>
<tr>
<th>Region of Interest (ROI)</th>
<th>n=ROI mentioned in results</th>
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<tbody>
<tr>
<td>PUC</td>
<td>13</td>
</tr>
<tr>
<td>CCGenu</td>
<td>13</td>
</tr>
<tr>
<td>CCSplen</td>
<td>13</td>
</tr>
<tr>
<td>ALIC</td>
<td>5</td>
</tr>
<tr>
<td>Cing., IFOF/ILF, CerebralP</td>
<td>4</td>
</tr>
<tr>
<td>CCBody, SLF</td>
<td>3</td>
</tr>
<tr>
<td>CR, Fornix, OR, CerebellarP, CST</td>
<td>2</td>
</tr>
<tr>
<td>EC</td>
<td>1</td>
</tr>
<tr>
<td>Global WM</td>
<td>4</td>
</tr>
</tbody>
</table>

ALIC, anterior limb of the internal capsule; CCBody, body of the corpus callosum; CCGenu, genu of the corpus callosum; CCSplen, splenium of the corpus callosum; CerebellarP, cerebellar peduncles; CerebralP, cerebral peduncles; Cing., cingulum; CR, corona radiata (superior); CST, corticospinal tract; EC, external capsule; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; NE, neonatal encephalopathy; OR, optic radiations; PLIC, posterior limb of the internal capsule; ROI, region of interest; SLF, superior longitudinal fasciculus.

For the 11 studies that reported on follow-up/outcomes, infants were assessed at time points ranging from 3 days to 3.5 years. Seven of these studies described four clinical assessment tests of global development; Bayley Scales of Infant Development (BSID), Griffiths Mental Development Scales (GMDS), Neonatal Behavioural Neurological Assessment (NBNA), NICU Network Neurobehavioural Scale (NNNS) and one clinical test applicable only to those neonates who developed cerebral palsy; Gross Motor Function Classification System (see table 3).17–19 23 25–27  The remaining four studies described other clinical tests including measurements of neuronal metabolism, follow-up MRI scans and other arbitrary scoring systems.28 30–32  Six of these studies were able to show an association between adverse outcomes and FA measurements in the PLIC and CC.18 23 25–27 31  Lower FA values in the PLIC were associated with more adverse outcomes, defined by poorer scores on various subsets of these clinical tests including the GMDS (development quotient), NBNA, NNNS (total motor score), BSID (psychomotor developmental index) and global developmental delay, as well as the development of cerebral palsy and/or epilepsy. Lower FA values in the CC were associated with more adverse outcomes, defined by poorer scores on the GMDS (development quotient) and BSID (mental developmental index). Not all infants were reported to have adverse outcomes, with several children with milder cases of NE showing normal development at follow-up.

DISCUSSION

The present review identifies three main white matter tracts of interest that appear to show altered levels of diffusion in infants with NE; the PLIC and the genu and splenium of the CC. Previously established scoring systems such as that of Barkovich6 classify NE injury in terms of damage to the basal ganglia/thalamus, and watershed cortical injury. Our identification of the PLIC as a ROI in NE fits in well with the basal ganglia/thalamus classification of injury, as it contains ascending and descending fibres that pass through the basal ganglia and separate the thalamus and the lenticular nucleus. Indeed, expanding on the work of Barkovich,9 Rutherford34 describes the presence of high signal intensity in the PLIC on a conventional T1-weighted MRI image, or the absence of low signal intensity in the PLIC on a conventional T2-weighted MRI image as an additional criteria for diagnosing NE. Usually myelinated at term, the PLIC can be seen as a low intensity signal on a T2-weighted scan in the healthy term infant. Loss of low signal or increased T2 signal within the PLIC may indicate evidence of NE, and in fact,

Figure 2  Tract ROIs as defined by JHU-ICBM DTI-81 white matter atlas, shown on the FMRIB58-FA template, in a sagittal (A), coronal (B) and axial (C) view. Tracts shown are those that arose as areas of interest in the literature search, with colour representing the relative amount of times that ROI was mentioned; ROIs in white being the most mentioned and ROIs in black being the least. The PLIC, genu and splenium of the corpus callosum (bright white) are the three ROIs that most appeared in the search. PLIC, posterior limb of the internal capsule; ROIs, regions of interest.
several of the studies reviewed included this as part of their diagnostic criteria.\textsuperscript{17, 18, 21, 22, 29}

Although not included as a classification of injury on conventional MRI images, the CC has recently been included in a novel scoring system for NE that also utilises DWI, developed by Weeke and colleagues.\textsuperscript{7} They assessed brain injury in terms of deep grey matter (including the basal ganglia, thalamus and PLIC), cerebral white matter (including the cortex, optic radiations and the CC), and the cerebellum. A large commissural fibre tract connecting the left and right hemispheres, the CC is thought to play a key role in cognitive\textsuperscript{35} and even motor\textsuperscript{36} functioning, deficits in which are often seen in NE infants later in life. It has in fact been shown that low apparent diffusion coefficient (ADC) values in the CC are associated with adverse outcome in NE infants at 18 months, and this association persisted (although to a lesser extent) in infants treated with therapeutic hypothermia.\textsuperscript{19, 20}

The clinical criterion for defining NE in the studies under review was fairly homogeneous, with most studies describing the NE infant as being born at term, with an Apgar score of 5 or less, metabolic acidosis (as defined by pH levels or base deficit) and/or a continued need for ventilation. All neonates included in the study were also all scanned within the first month of life. Despite this consistency however, DWI has been shown to vary considerably even over the first few days and weeks of life.\textsuperscript{38} DWI is the most sensitive MRI sequence for imaging the encephalopathiuc within the first few days following the hypoxic-ischaemic event, as T1-weighted and T2-weighted images can produce false negatives at this time. However, at approximately 1 week of age for normothermic infants and between approximately 11–12 days for infants treated with therapeutic hypothermia, DWI may underestimate the extent of the brain injury due to the phenom- enon of pseudonormalisation.\textsuperscript{19, 40} While the ADC is initially decreased in NE infants within the first few hours following an acute brain injury, by the end of the first week of life the ADC increases to reach apparently normal levels. It is therefore key that we take into account the careful timing of DWI in our prospective study going forward, to produce the most accurate representation of the damage. Ideally, neonates should be imaged between days 3 and 7 of life, for diffusion changes to be fully assessed in NE.

There was heterogeneity in the study populations under review, due mainly to the small number of studies conducted in this area, which meant the inclusion of infants with varying severity of NE (mild, moderate, severe) and infants that had and not been treated with therapeutic hypothermia. This is likely to have added bias to the study due to the possibility that infants treated with therapeutic hypothermia and infants managed at normothermia may show differing diffusion measures. It will therefore be critical to consider and identify any possible subgroups in a prospective study, including severity of NE and treatment interventions. This will be especially crucial when attempting to relate diffusion measures to neurodevelopmental outcome. Outcome variables were only obtained for 13 of the reviewed studies; however, it is only through the long-term follow-up of these infants that we can discern the prognostic value of DWI/DTI in NE.

It should also be noted that, although this review focused solely on diffusion changes in the white matter tracts of the brain, DWI can also demonstrate detectable changes in the deep grey matter, in particular the basal ganglia and the thalamus. Reduced ADC in these regions has been found in infants with severe NE, and these values may be informative of adverse neurodevelopmental outcome and the development of dyskinetic cerebral palsy.\textsuperscript{41} A prospective study should therefore not only examine diffusion measures in the white matter tracts but also the deep grey matter structures of the NE infant brain.

**CONCLUSIONS**

The addition of DWI/DTI to the scanning protocol within the first week of life can be an excellent method to assess brain injury in neonates with NE. In particular, specific attention should be placed on obtaining FA measures in areas such as the PLIC and the genu and splenium of the CC. These data may then be used to assess the impact of therapeu- tic hypothermia on the injury, and as a prognostic tool to predict possible neurodevelopmental outcomes.

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**Contributors** ALWB and EA conceived the idea for the work, MD acquired the data and performed analysis, all authors contributed to the interpretation of the data. MD and ALWB initially drafted the manuscript and all authors provided critical revisions of the work. All authors approved final version of work for submission, and agree to be accountable for all aspects of the work.

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