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). Affecting approximately two to six in every 1000 live births, 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. Moderate–severe NE is associated with adverse outcomes (long-term morbidity and mortality) at a rate of approximately 50%. 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 problematic behaviour. 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.

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.

Correspondence to
Megan Dibble, Cognitive Systems Group, Discipline of Psychiatry, School of Medicine, Trinity College Dublin, Dublin 2, Ireland; dibblem@tcd.ie

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systems have been developed for the assessment of NE. The most widely known and used is the Barkovich scoring system, 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, 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. 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.

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 (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements. 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 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 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 FMRI58 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. These studies all met the guidelines outlined in the STROBE statement in regard to quality and bias. Follow-up/outcomes were available in 11 of these studies. 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. 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).
Table 1 Data extracted from the literature for the main variables of interest

<table>
<thead>
<tr>
<th>Authors</th>
<th>Definition/criteria</th>
<th>Groups</th>
<th>Age at scan</th>
<th>mRI/other scans with DWI scan</th>
<th>Metrics</th>
<th>Conventional MRI findings/scoring criteria</th>
<th>Outcomes</th>
<th>Whole brain/ROI</th>
<th>Reported findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porter et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>▶ Born at 36 weeks GA or after&lt;br&gt;▶ Apgar score of 5 or less or continued need for resuscitation within 10 min of birth or acidosis within 60 min after birth&lt;br&gt;▶ Moderate-to-severe encephalopathy (lethargy, stupor or coma)&lt;br&gt;▶ One or more hypertonia, abnormal reflexes, absent week suck, clinical seizures&lt;br&gt;▶ Abnormal EEG activity of at least 30 min&lt;br&gt;▶ Unrected HIE and coated HIE and healthy term</td>
<td>1–21 days</td>
<td>10/10/8 FA – –</td>
<td>Whole brain—TBSS</td>
<td>FA – –</td>
<td>–</td>
<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&lt;br&gt;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, thalamus, globus pallidus, and putamen.</td>
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<tr>
<td>Lally et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>▶ Born at 36 weeks GA or after&lt;br&gt;▶ Apgar score of 5 or less or continued need for resuscitation within 10 min of birth or acidosis within 60 min after birth&lt;br&gt;▶ Moderate-to-severe encephalopathy (lethargy, stupor or coma)&lt;br&gt;▶ One or more hypertonia, abnormal reflexes, absent week suck, clinical seizures&lt;br&gt;▶ Abnormal EEG background for min 30&lt;br&gt;▶ HIE and healthy term</td>
<td>Within 3 weeks</td>
<td>31 FA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Whole brain—TBSS and ROI: CCgenu, CCsplen, CSTs, left and right temporal and periventricular areas</td>
<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&lt;br&gt;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&lt;br&gt;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, thalamus, globus pallidus, and putamen.</td>
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<tr>
<td>Turos et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>▶ Born at 36 weeks GA or after&lt;br&gt;▶ Apgar score of 5 or less or continued need for resuscitation within 10 min of birth or acidosis within 60 min after birth&lt;br&gt;▶ Moderate-to-severe encephalopathy (lethargy, stupor or coma)&lt;br&gt;▶ One or more hypertonia, abnormal reflexes, absent week suck, clinical seizures&lt;br&gt;▶ Abnormal EEG background for min 30&lt;br&gt;▶ HIE (Severe)</td>
<td>Within 3 weeks</td>
<td>40</td>
<td>FA</td>
<td>40 had WM injury&lt;br&gt;11 had cortical abnormalities&lt;br&gt;12 had BGT injury&lt;br&gt;12 had abnormal/high signal in the PML&lt;br&gt;44 had abnormal/minimal signal in the frontal lobes&lt;br&gt;28 had abnormal/high signal in the PLIC</td>
<td>38 seen for follow-up&lt;br&gt;Abnormal outcome in 16/88 (18% of mild, 50% of moderate, 100% of severe)&lt;br&gt;Three had cerebral palsy&lt;br&gt;Four had Bayley-Motor &lt; 80&lt;br&gt;One had abnormal vision&lt;br&gt;Nine had a fall in occipital-frontal circulmference&lt;br&gt;Three had ongoing need for anti-epileptics</td>
<td>Whole brain—TBSS</td>
<td>Significantly lower FA values were seen in the following regions: the corona radiata, posterior limb of the internal capsule, periventricular region, posterior limb of the anterior commissure, and thalamus.</td>
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<tr>
<td>Seo et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>▶ Appar score less than 5 at birth&lt;br&gt;▶ 5 and 5 min after birth, or umbilical cord, amnial or capillary pH less than 7.2, or base deficit of at least 16 mM within 1 hour after birth&lt;br&gt;▶ HIE and healthy term</td>
<td>36–44 weeks PCA</td>
<td>27/35</td>
<td>FA, AD, RD</td>
<td>20 had normal cMRI&lt;br&gt;20 had normal MRI&lt;br&gt;Two had BGT injury&lt;br&gt;Two had watershed without BGT injury&lt;br&gt;Three had WM abnormalities with hyperintensity in the CCgenu and splen&lt;br&gt;24 seen for follow-up&lt;br&gt;16 normal&lt;br&gt;Six had an abnormal tone, motor problems or developmental delay (GMFCS-R)&lt;br&gt;Whole Brain—TBSS</td>
<td>A group difference in the FA and RD between the normal and HIE was seen in the AC, AUC, CS, CCgenu, RO, right IJ, PML, SLF and CCsplen&lt;br&gt;Correlation between locomotor function and FA was not observed.</td>
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### Table 1 Continued

<table>
<thead>
<tr>
<th>Authors</th>
<th>Definition/criteria</th>
<th>Groups</th>
<th>Age at scan</th>
<th>n-Neonates with DWI scan</th>
<th>Conventional MRI findings/scoring criteria</th>
<th>Outcomes</th>
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<tr>
<td>Gao et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Evidence of fetal distress (heart rate abnormalities or meconium stained amniotic fluid) or neonatal distress (umbilical cord pH less than 7.2 and/or age less than 7 within 1 min of birth)</td>
<td>Mild HIE and healthy term</td>
<td>Within 28 days</td>
<td>24/17 FA, 3, 3, 3</td>
<td>FA, J, 1, 2, 3</td>
<td>Whole brain—TBS</td>
<td>FA values related to lower fiber numbers in the SLFs, PLICs and ALICs showed statistically significant differences between the moderate and severe HIE groups, and were significantly different between the control and moderate groups.</td>
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<tr>
<td>Kline-Fath et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Metabolic acidosis (pH less than 7.1 and/or base deficit less than 10).</td>
<td>HIE with seizures and HIE without seizures</td>
<td>Within 2 weeks</td>
<td>25/23 FA</td>
<td>FA</td>
<td>RO: CCgenu, CCsplen, PLIC, ALC</td>
<td>MO: Neurological exam consistent with HIE—scores significantly different among the three groups, lowest scores in severe HIE and correlation coefficient highest for the PLIC.</td>
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<tr>
<td>Carrasco et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Diagnosis of moderate to severe HIE</td>
<td>Cooked HIE</td>
<td>Within 10 days</td>
<td>25</td>
<td>FA</td>
<td>ROI: thalamus, basal ganglia, PLIC, antCS, postCS, cerebellum WM, pons</td>
<td>MO: Neurovascular injury in white matter, basal ganglia, posterior limb of internal capsule and watershed areas compared with the group without seizures.</td>
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<tr>
<td>Li et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Diagnosis and inclusion criteria were in accordance with HIE diagnostic criteria and clinical classification of practical neonatal HIE</td>
<td>Moderate HIE and severe HIE and healthy term</td>
<td>10–14 days</td>
<td>14/10</td>
<td>ADC, IA</td>
<td>RO: 20 inducing the PLIC, ALC, bilateral paresthesia, deep WM of frontal lobes, CCgenu, CCsplen, head of caudate nucleus, thalamus, thalamus, pons</td>
<td>ADC: 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.</td>
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Key:
- **FA**: Fractional Anisotropy
- **ADC**: Apparent Diffusion Coefficient
- **MO**: Modified Observer Assessment Scale
- **RO**: Regions of interest
- **SLFs**: Superior longitudinal fasciculus
- **PLIC**: Posterior limb of internal capsule
- **ALIC**: Anterior limb of internal capsule
- **Carrasco**: Carrasco et al.
- **Fath**: Fath et al.
- **Kline**: Kline-Fath et al.
- **Gao**: Gao et al.
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<th>Reported findings</th>
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<tr>
<td>Lemmon et al.</td>
<td>pH of 7.0 or less or base deficit of 16 or more within 1 hour of birth</td>
<td>Cooled HIE and healthy term</td>
<td>1–28 days</td>
<td>57/12</td>
<td>FA, MD</td>
<td>Barkovich scoring (1) normal</td>
<td>RO: bilateral thalamus, superior, middle, and inferior CPs, and the dentate nucleus</td>
<td>FA value of thermal cerebellar peduncles and MD values of the superior cerebellar peduncles were significantly lower in patients with evidence of moderate or severe injury on MRI than in controls.</td>
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<tr>
<td>Mosiano et al.</td>
<td>Diagnosis of perinatal asphyxia or hypoxic-ischemic encephalopathy</td>
<td>Cooled HIE</td>
<td>7–10 days</td>
<td>45</td>
<td>FA, MD, A2 RD</td>
<td>Barkovich scoring: mild, moderate, severe</td>
<td>RO: cerebellar peduncles, PLIC, CS, CC</td>
<td>Significant associations were observed between DTI corticospinal tract integrity and NMS in postmortem-injured HIE newborns.</td>
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<td>Ancora et al.</td>
<td>Birth asphyxia</td>
<td>Cooled HIE</td>
<td>4–16 days</td>
<td>15</td>
<td>FA, MD, A1, A2, A3</td>
<td>Barkovich scoring: normal, WS, B.</td>
<td>RO: supratentorial region, posterior cerebral artery, deep white matter, and posterior thalamus</td>
<td>MD showed significantly decreased values in many regions of white and grey matter, suggesting decreased oxidative metabolism.</td>
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<tr>
<td>Gano et al.</td>
<td>Diagnosis of perinatal asphyxia or hypoxic-ischemic encephalopathy</td>
<td>HIE</td>
<td>3 days</td>
<td>19</td>
<td>FA, MD</td>
<td>Barkovich scoring: normal, WS, B, N,</td>
<td>RO: anterior part of the brain,</td>
<td>In grey matter, MD and metabolite ratios measured on day 1 were predictive of neurological abnormalities.</td>
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<tr>
<td>Wendt et al.</td>
<td>Abnormal fetal heart rate patterns</td>
<td>HIE and healthy term</td>
<td>Within 3 weeks</td>
<td>2017</td>
<td>ADC, BA, IA</td>
<td>B/GT grading normal, mild,</td>
<td>RO: CS (central), bilateral lenticulostriate, mediodorsal thalami, ventrolateral nuclei of thalamus, PLIC, B.</td>
<td>During the first week, FA values were decreased with both severe and moderate B/GT injury and some severe B/GT injury.</td>
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<td>van Pul et al.⁷</td>
<td>Clinical symptoms of NE present in first 3 days of life together with two or more of fetal heart rate, breathing, and/or muscle movements. Unilateral or bilateral (on film, less than 7.0), meconium stained fluid, Agar score below 5 minimum not less than 7.</td>
<td>HIE</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 ms. In six infants (seven) tissue loss or signal intensity abnormalities observed in the region of lesion, with abnormalities in the basal ganglia in 2, and mild delayed delayed myelination in 2. In both infants without abnormalities in the region of the lesion, myelination was delayed. Severe neurodevelopmental delay in three children, or visual impairment in one child. Normal development observed in 2 children at 1 and in 1 at 6Y</td>
<td>ROIs: CC and WM</td>
<td>Changes in lesions were characterized by a decrease in ADC (40%) in all regions, with a stronger decrease in the direction perpendicular to the fibres, resulting in increased anisotropy index. The relative change in anisotropy decreased linearly with time, with the strongest effect in the anterior white matter.</td>
</tr>
<tr>
<td>Al Amrani et al.¹⁵</td>
<td>Born at 36 weeks GA or after evidence of fetal distress, for example, history of antepartum event, cord prolapse or fetal death ≤16, or continued need for ventilator support at birth for ≥10 min.</td>
<td>Cooled HIE</td>
<td>10 days</td>
<td>29</td>
<td>ADC, IA</td>
<td>Barkovitch scoring 0 (no brain injury), 1 (focal cortical injury pattern), 2 (focal watershed injury pattern) and 3 to 4 (neurological injury pattern)</td>
<td>Adverse outcomes: cerebral palsy, global developmental delay, epilepsy. In neonates who developed an adverse outcome, ADC values significantly decreased on days 2–3 of life and increased around day 10 of life in the thalamus, PLIC, and lentiform nucleus. Then, ADC values increased (pseudonormalisation) and FA decreased around day 10 in the same ROIs.</td>
<td>ROIs: thalamus, PLIC, lentiform nucleus, front and post-WM, cortical GM</td>
<td>Among the newborns developing adverse outcome, ADC values were significantly decreased on days 2–3 of life and increased around day 10 of life in the thalamus, PLIC, and lentiform nucleus. FA values decreased in the same regions around day 30 of life. These newborns also had increased ADC around days 10 and 30 of life, and decreased FA around day 30 in the anterior and posterior WM.</td>
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<tr>
<td>Kansagra et al.¹³</td>
<td>Birth at 36 weeks GA or after moderate or severe HE.</td>
<td>Newborn NE and 6-month NE</td>
<td>0 months and 6 months</td>
<td>12</td>
<td>FA, NOD, OD, FW (NODD)</td>
<td>–</td>
<td>Infants assigned a validated neonate motor 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 severe quadriparesis. All infants had scores of 0 or 1 at an average 5.9 days.</td>
<td>ROIs: PLIC, AUC, OR, CCgenu, CCpulsen</td>
<td>At birth, the CC collectively demonstrated significantly higher FA than the AUC or OR. Moreover, the CC demonstrated significantly lower OD and higher FW than the PLIC, AUC or optical radiations at birth. Measured FA was significantly higher at 6 months than at birth within all measured white matter tracts. In contrast, OD was significantly higher only within the PLIC, AUC and or PLIC OR and OD; OD was significantly higher only within the AUC and OR. Measured FW was significantly lower at 6 months than at birth within the OR, genu and or PLIC.</td>
</tr>
<tr>
<td>Law et al.¹⁶</td>
<td>Retrospective diagnosis of NE, all cooled.</td>
<td>NE (normal MRI) and NE (abnormal MRI) and healthy premature at term equivalent</td>
<td>5–18 days</td>
<td>122/4/12</td>
<td>ADC, IA</td>
<td>11 had predominantly IGT injury without WM injury. Four had predominantly diffuse cortical injuries with underlying WM injury. There were no significant differences in measured FA in white matter between the NNE and the control group.</td>
<td>11 had predominantly IGT injury without WM injury. Four had predominantly diffuse cortical injuries with underlying WM injury. There were no significant differences in measured FA in white matter between the NNE and the control group.</td>
<td>ROIs: PLIC, temporal, occipital, parietal and frontal WM, CCgenu, CCpulsen</td>
<td>We found significant reductions in measured FA in white matter within the ANE neonates compared with the control group. There were, however, no significant differences in measured FA in white matter between the NNE and the control group. The FA of CCgenu and CCpulsen was the lowest in the thalamic pattern, followed by the posterior WM and the basal ganglia pattern.</td>
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</table>

ADC, apparent diffusion coefficient; AUC, anterior limb of the internal capsule; ANE, anoxic encephalopathy; axial diffusion tensor imaging; CC, corpus callosum; CT, computed tomography; DW, diffusion weighted imaging; FA, fractional anisotropy; FW, free water fraction; GM, glucose-6-phosphate; MRI, magnetic resonance imaging; NE, neonatal encephalopathy; NNE, neonatal neonatal encephalopathy; OD, outer domain; OR, optic radiations; PCA, postconceptional age; PLIC, posterior limb of the internal capsule; PP, peripartum; ROI, regions of interest; SLF, superior longitudinal fasciculus; TBSS, tract-based spatial statistics; WM, white matter.
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>
</tr>
</thead>
<tbody>
<tr>
<td>PLIC</td>
<td>13</td>
</tr>
<tr>
<td>CC Genu</td>
<td>13</td>
</tr>
<tr>
<td>CC Splen</td>
<td>13</td>
</tr>
<tr>
<td>ALIC</td>
<td>5</td>
</tr>
<tr>
<td>Cing., IFOF/ILF, Cerebellar P</td>
<td>4</td>
</tr>
<tr>
<td>CCB, Body, SLF</td>
<td>3</td>
</tr>
<tr>
<td>CR, Fornix, OR, Cerebellar P, CST</td>
<td>2</td>
</tr>
<tr>
<td>EC</td>
<td>1</td>
</tr>
<tr>
<td>Global WM</td>
<td>4</td>
</tr>
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</table>

ALIC, anterior limb of the internal capsule; CCB, body of the corpus callosum; CC Genu, genu of the corpus callosum; CC Splen, splenium of the corpus callosum; Cerebellar P, cerebellar peduncles; Cerebral P, 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 21 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 Barkovich 6 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, 6 Rutherford 34 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,
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 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{37}

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 encephalopathic 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 phenomenon 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 had 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 therapeutic hypothermia on the injury, and as a prognostic tool to predict possible neurodevelopmental outcomes.

Twitter Tim Hurley @timphurley

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**ORCID iDs**

Tim Hurley http://orcid.org/0000-0003-0069-6362

Eleanor J Molloy http://orcid.org/0000-0001-6798-2158

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