

# Diffusion tensor imaging in neonatal encephalopathy: a systematic review

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## 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).<sup>1</sup> Affecting approximately two to six in every 1000 live births,<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> Previously, it was thought that

## 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.

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.<sup>5</sup>

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.<sup>5</sup> 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



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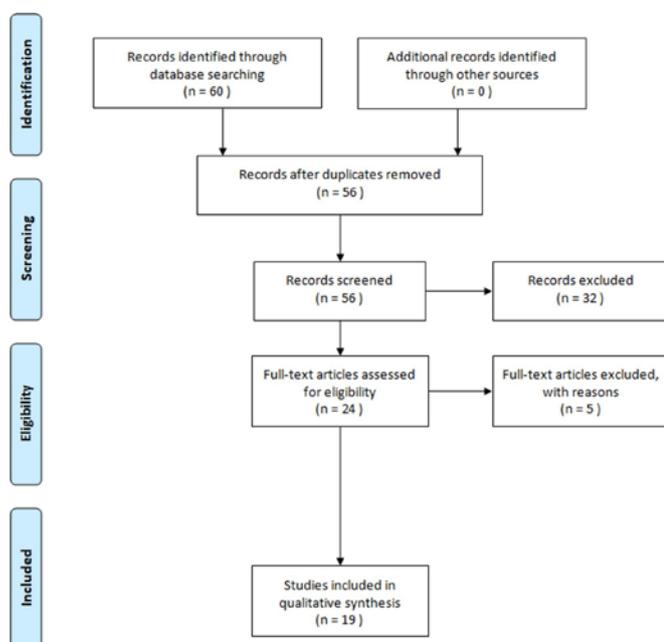
systems have been developed for the assessment of NE. The most widely known and used is the Barkovich scoring system,<sup>6</sup> in which T1-weighted and T2-weighted images are assessed to grade the damage to the brain in NE infant in terms of basal ganglia/thalamus injury, and watershed cortical injury. Recent MRI scoring systems, such as that of Weeke and colleagues,<sup>7</sup> 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.<sup>8</sup> 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 or not yet show any abnormalities in the first week of life<sup>9</sup>; 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.<sup>10</sup>

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<sup>11</sup> and Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) statements.<sup>12</sup> 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



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the search and selection process.

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<sup>13</sup> 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<sup>14</sup> 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 FSLeys (<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.<sup>15–33</sup> These studies all met the guidelines outlined in the STROBE statement<sup>13</sup> in regard to quality and bias. Follow-up/outcomes were available in 11 of these studies.<sup>17–19 23 25–28 30–32</sup> 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.<sup>15</sup> 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

| Authors                           | Definition/criteria  | Groups  | Age at scan     | n=Neonates with DWI scan | Metrics    | Conventional MRI findings/scoring criteria   | Outcomes   | Whole brain/ROI  | Reported findings  |
|-----------------------------------|--|---|-----------------|--------------------------|------------|--|--|--|--|
| Porter <i>et al</i> <sup>15</sup> | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Apgar score of 5 or less</li> <li>or continued need for resuscitation within 10 min of birth OR acidosis within 60 min after birth</li> <li>Moderate-to-severe encephalopathy (lethargy, stupor or coma)</li> <li>One or more of hypotonia, abnormal reflexes, absent/weak suck, clinical seizures</li> <li>Abnormal EEG activity of at least 30 min</li> </ul> | Untreated HIE and cooled HIE and healthy term         | 1–21 days       | 10/108                   | FA         | –  | –  | Whole brain—TBSS   | <ul style="list-style-type: none"> <li>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</li> <li>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</li> </ul>  |
| ly <i>et al</i> <sup>16</sup>     | –  | HIE and healthy term                                  | 2–10 days       | 12/11                    | FA         | –  | –  | Whole brain—TBSS and ROI: CCgenu, CCsplen, CSTs, left and right temporal and periventricular areas | 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  |
| Lally <i>et al</i> <sup>17</sup>  | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Resuscitation at birth and/or within 5 min of birth, and Thompson encephalopathy score of less than 6 within 6 hours of birth</li> </ul>  | NE (Samat graded)                                     | Within 3 weeks  | 31                       | FA         | <ul style="list-style-type: none"> <li>40 had WM injury</li> <li>31 had cortex abnormalities</li> <li>12 had BGT injury</li> <li>Five had absence of high signal in the PLIC</li> </ul>  | <ul style="list-style-type: none"> <li>38 seen for follow-up</li> <li>Abnormal outcome in 16/38 (33% of severe)</li> <li>Three had cerebral palsy</li> <li>Four had Bayley-III &lt;85</li> <li>One had abnormal vision</li> <li>Nine had a fall in occipital-frontal circumference</li> <li>Three had ongoing need for anti-epileptics</li> </ul>  | Whole brain—TBSS   | <ul style="list-style-type: none"> <li>Abnormalities were frequently observed in white matter (n=40, 91%) and cortex (n=31, 70%) while only 12 (27%) had abnormal basal ganglia/thalami</li> <li>Those infants with moderate/severe encephalopathy had globally reduced FA compared with the rest of the cohort</li> <li>Reduced white matter FA was associated with Samat stage deep grey nuclear injury and MR spectroscopy N-acetylaspartate/ choline, but not early Thompson scores</li> <li>Of the surviving babies, 42% had adverse neurodevelopmental outcomes</li> </ul>   |
| Tuson <i>et al</i> <sup>18</sup>  | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Apgar score of 5 or less or continued need for resuscitation within 10 min of birth OR acidosis within 60 min after birth</li> <li>Moderate-to-severe encephalopathy (lethargy, stupor or coma)</li> <li>One or more of hypotonia, abnormal reflexes, absent or weak suck, clinical seizures</li> <li>Abnormal EEG background for min 30 min</li> </ul>         | HIE (fulfilling criteria for therapeutic hypothermia) | Within 3 weeks  | 43                       | FA         | <ul style="list-style-type: none"> <li>27 had BGT injury (12 severe)</li> <li>20 had PLIC abnormalities</li> <li>WM abnormalities present in all but 2</li> <li>21 had cortex abnormalities</li> </ul>                         | <ul style="list-style-type: none"> <li>18 had unfavourable outcomes, including nine who died</li> <li>Six had GMDs-R (DQ) scores &lt;2 SD below the mean; 2 of which developed cerebral palsy (GMFCS level III-IV) and two were diagnosed with cerebral palsy (GMFCS level V)</li> <li>Lower FA in infants that went on to have unfavourable outcomes</li> <li>Correlation between locomotor function and FA values in the CC and CSTs</li> <li>Correlation between DQ scores and FA values in the fornix, cingulum and uncinate fasciculus</li> </ul> | Whole brain—TBSS   | <ul style="list-style-type: none"> <li>Significantly lower FA values were seen in infants who went on to have unfavourable outcomes as compared with those who had favourable outcomes</li> <li>These lower values of FA were seen in several regions of the brain, including the right centrum semiovale, splenium, isthmus and genu of the CC, anterior limb of the internal capsule, PLIC, external capsules, optic radiations, cerebral peduncles, fornix, cingulum, and inferior longitudinal fasciculus</li> <li>The GMDs-R showed a significant linear correlation between FA values and developmental quotient (DQ) and all its component subscale scores</li> </ul> |
| Seo <i>et al</i> <sup>19</sup>    | <ul style="list-style-type: none"> <li>Apgar score less than 5 both 1 and 5</li> <li>or arterial or capillary pH less than 7.0, or base deficit of at least 16 mM within 1 hour after birth</li> </ul>   | HIE and healthy term                                  | 36–44 weeks PCA | 27/95                    | FA, AD, RD | <ul style="list-style-type: none"> <li>20 had normal CMRI</li> <li>Two had BGT injury</li> <li>Two had watershed without BGT injury</li> <li>Three had WM abnormalities with hypo-intensity in the CCgenu and splen</li> </ul> | <ul style="list-style-type: none"> <li>24 seen for follow-up</li> <li>18 normal</li> <li>Six had an abnormal tone, motor problems or developmental delay (GMDs-R)</li> </ul>   | Whole Brain – TBSS   | <ul style="list-style-type: none"> <li>A group difference in the FA and RD between the normal and HIE was seen in the A.C., ALIC, CS, CCgenu, FO, right ILF, PLIC, SLF and CCsplen</li> </ul>  |

Continued

Table 1 Continued

| Authors                               | Definition/criteria  | Groups                                       | Age at scan    | n=Neonates with DWI scan | Metrics                                     | Conventional MRI findings/scoring criteria   | Outcomes   | Whole brain/ROI  | Reported findings  |
|---------------------------------------|--|--|----------------|--------------------------|---|--|--|--|--|
| Gao <i>et al</i> <sup>60</sup>        | <ul style="list-style-type: none"> <li>Evidence of fetal distress (fetal rate 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)</li> <li>Clinical signs of NE in first 72 hours after delivery (abnormal consciousness, abnormal muscular tension, weak/absent primary reflexes, abnormal MR)</li> </ul> | Mild HIE and healthy term                    | Within 28 days | 24/17                    | FA, $\lambda_1$ , $\lambda_2$ , $\lambda_3$ | Mild HIE injuries were presented as punctate WM injury with hyperintensity in T1WIs and hypointensity in T2WIs and watershed WM injury with hypointensity in T1WIs and hyperintensity in T2WIs   | –  | Whole brain—TBSS   | <ul style="list-style-type: none"> <li>We found decreased FA in CP, PLIC and CR in all injured neonates.</li> <li>Decreased FA and increased <math>\lambda_2</math>, <math>\lambda_3</math> in CST, CCgenu, EC and CCsplen in mild HI neonates.</li> <li>Regions with FA decreases were accompanied by increased <math>\lambda_2</math> and <math>\lambda_3</math> (ie, increased radial diffusivity), while the <math>\lambda_1</math>, which contributes to axial diffusivity and reflects the number and diameter of axons, exhibit no obvious changes</li> <li>These findings suggested that such mild HI white matter injury mainly led to deficits or delays in myelination, instead of damage on axons</li> </ul> |
| Kline-Fath <i>et al</i> <sup>61</sup> | <ul style="list-style-type: none"> <li>Metabolic acidosis (pH less than 7.1 and/or base deficit less than 15).</li> <li>Apgar score of 5 or less within 5 min of birth</li> <li>Prolonged resuscitation</li> <li>Neurological exam consistent with HIE</li> <li>Group with and group without clinical seizures.</li> <li>Abnormal EEG background</li> </ul>  | HIE with seizures and HIE without seizures   | Within 2 weeks | 25/23                    | FA  | <ul style="list-style-type: none"> <li>MRI scans were graded for injury in watershed areas, BGT and PLIC</li> <li>We additionally graded for injury in brainstem, cerebellum, WM, parenchymal cortex and hippocampus</li> </ul>  | –  | ROI: CCgenu, CCsplen, PLIC, ALIC   | <ul style="list-style-type: none"> <li>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</li> <li>The severity of injury in all measured areas increased with increasing seizure severity</li> <li>The seizure group also had lower FA values in PLIC and the splenium of CC</li> </ul>  |
| Carrasco <i>et al</i> <sup>62</sup>   | <ul style="list-style-type: none"> <li>Born at 35 weeks GA or after</li> <li>Diagnosis of moderate to severe HIE</li> </ul>  | Cooled HIE                                   | Within 10 days | 25                       | MD  | NRN 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 | –  | ROI: thalamus, basal ganglia, PLIC, antCS, postCS, cerebellar WM, pons   | <ul style="list-style-type: none"> <li>Neonates with blood pressure measurements within optimal MAP during rewarming had less brain injury by NRN score</li> <li>Longer duration of MAP within optimal MAP during hypothermia correlated with higher mean diffusivity in the anterior centrum semiovale and pons</li> <li>Blood pressure deviation below optimal MAP was associated with lower mean diffusivity in cerebellar white matter</li> <li>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</li> </ul>   |
| Li <i>et al</i> <sup>63</sup>         | <ul style="list-style-type: none"> <li>Diagnosis and inclusion criteria were in accordance with HIE diagnostic criteria and clinical classification of practical neonatal HIE</li> </ul>   | Moderate HIE and severe HIE and healthy term | 10–14 days     | 14/8/10                  | ADC, FA                                     | <ul style="list-style-type: none"> <li>NBNA at 15 days (behavioural ability, active and passive muscle tension, primitive reflex and evaluation of general condition)—scores significantly different among the three groups, lowest scores in severe HIE and correlation coefficient highest for the PLIC</li> </ul>   | <ul style="list-style-type: none"> <li>NBNA at 15 days (behavioural ability, active and passive muscle tension, primitive reflex and evaluation of general condition)—scores significantly different among the three groups, lowest scores in severe HIE and correlation coefficient highest for the PLIC</li> </ul> | ROI: 20 including the PLIC, ALIC, bilateral parietal cortex, deep WM of frontal lobe, CCgenu, CCsplen, head of caudate nucleus, lenticular nucleus, thalamus, pons | <ul style="list-style-type: none"> <li>FA values in the PLICs and in the thalami showed statistically significant differences between the moderate and severe groups, and were significantly different between the control and moderate groups</li> <li>Voxel volumes in the SLFs, PLICs and ALICs showed statistically significant differences between the moderate and severe HIE groups</li> <li>The fibre numbers in the PLICs, cingulate gyrus, IFLs and IFOFs were significantly different between the moderate and severe HIE groups</li> <li>NBNA scores were significantly different among the three groups, with the severe HIE group having the lowest scores</li> </ul>                                      |

Continued

Table 1 Continued

| Authors                            | Definition/criteria  | Groups                      | Age at scan    | n=Neonates with DWI scan | Metrics                           | Conventional MRI findings/scoring criteria  | Outcomes   | Whole brain/ROI  | Reported findings  |
|------------------------------------|--|-----------------------------|----------------|--------------------------|-----------------------------------|---|--|--|--|
| Lemmon <i>et al</i> <sup>84</sup>  | <ul style="list-style-type: none"> <li>pH of 7.0 or less or base deficit of 16 or more within 1 hour of birth</li> <li>Acute perinatal event</li> <li>Apgar score of 5 or less within 10 min of birth or assisted ventilation at birth for at least 10 min</li> <li>Required hypothermia without discontinuation before 72 hours</li> </ul>                                    | Cooled HIE and healthy term | 1–28 days      | 57/12                    | FA, MD                            | <ul style="list-style-type: none"> <li>Barkovich scoring: (1) normal WM (T2-hyperintense signal or restricted diffusion) (3) moderate: injury of BGT or cortex (4) severe: injury of BGT and cortex</li> </ul>  | –  | ROI: bilateral thalami, superior, middle, and inferior CPs, and the dentate nucleus  | <ul style="list-style-type: none"> <li>FA values of the middle 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</li> <li>In patients, cerebellar DTI scalars correlated positively with DTI scalars within the thalami</li> </ul>         |
| Massaro <i>et al</i> <sup>85</sup> | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Weight 1800 g or greater at birth</li> <li>Metabolic acidosis and/or low Apgar scores</li> <li>Signs of moderate/severe NE</li> </ul>   | Cooled HIE                  | 7–10 days      | 45                       | FA, MD, AD, RD                    | <ul style="list-style-type: none"> <li>Barkovich scoring: BG and WS</li> <li>Miller scoring for WM: mild, moderate, severe</li> </ul>   | <ul style="list-style-type: none"> <li>NNNS: motor performance and cognitive/behavioural functioning—infants with severe MRI injury obtained worse scores compared with those without BSID-II at min 21 months</li> </ul>  | ROI: cerebral peduncle, PLIC, CS, CC   | <ul style="list-style-type: none"> <li>Significant associations were observed between DTI corticospinal tract integrity and NNNs</li> <li>Neonatal neuromotor performance was also related to later early childhood motor outcomes</li> </ul>  |
| Massaro <i>et al</i> <sup>86</sup> | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>&gt;1800 g at birth</li> <li>Metabolic acidosis and/or low Apgar scores</li> <li>Signs of moderate-to-severe clinical encephalopathy</li> </ul>   | Cooled HIE                  | 7–10 days      | 50                       | FA, MD, AD, RD                    | <ul style="list-style-type: none"> <li>Barkovich scoring: BGW score ranging from 0 to 4</li> </ul>  | <ul style="list-style-type: none"> <li>Bayley-II: association between CST FA and Psychomotor Developmental Index (PDI), association between CC FA and Mental Developmental Index (MDI)</li> </ul>  | ROI: CSTs in the CP, PLIC, CS, CC  | <ul style="list-style-type: none"> <li>Lower CC and CST FA were associated with lower MDI and PDI, respectively</li> <li>There was also a direct relationship between CC axial diffusivity and MDI, while CST radial diffusivity was inversely related to PDI</li> </ul>   |
| Anzora <i>et al</i> <sup>87</sup>  | <ul style="list-style-type: none"> <li>Born at term</li> <li>Moderate or severe HIE (Sarnat)</li> </ul>  | Cooled HIE                  | 4–16 days      | 15                       | FA, MD, $\lambda_1$ , $\lambda_2$ | <ul style="list-style-type: none"> <li>Barkovich scoring: abnormal signal in deep grey matter nuclei detected in seven infants, and changes in the watershed regions also present in 4</li> </ul>   | <ul style="list-style-type: none"> <li>Six showed a poor outcome</li> <li>One with severe HIE died</li> <li>Four developed cerebral palsy, one of whom died at 1.8m</li> <li>One developed severe hearing loss</li> <li>Normal psychomotor outcome in remaining patients (GMDS)</li> </ul> | ROI: supratentorial region, posterior cranial fossa, CCgenu, CCsplen, caudate, PLIC, thalamus, lenticular nucleus, optic radiation, occipital WM, frontal WM, fronto-parietal WM | <ul style="list-style-type: none"> <li>MD showed significantly decreased values in many regions of white and grey matter, axial diffusivity showed the best predictive value in the genu of CC, and radial diffusivity was significantly decreased in fronto white matter and fronto parietal WM</li> <li>The decrement of FA showed the best AUC in the FPWM</li> </ul> |
| Gano <i>et al</i> <sup>88</sup>    | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Clinically recognisable encephalopathy</li> <li>One or more of fetal distress at delivery, requirement for resuscitation at birth, Apgar score <math>\leq 5</math> at 5 min and metabolic acidosis (umbilical artery pH &lt;7.1 or base deficit &gt;10)</li> </ul>                                | HIE                         | 3 days         | 19                       | FA, MD                            | <ul style="list-style-type: none"> <li>Barkovich scoring: normal, WS, BN, total and focal-multifocal injury</li> </ul>  | <ul style="list-style-type: none"> <li>Therapeutic hypothermia associated with an attenuated reduction of MD in GM and WM from days 1 to 3</li> <li>Hypothermia also associated with increased neuronal metabolism and WM integrity, as well as reduced oxidative metabolism</li> </ul>    | ROI: ant and post WS white matter, CSTs in the CS, CC, PLIC, ORs, caudate, putamen, ventrolateral thalami, calcareine region, and hippocampi                                     | <ul style="list-style-type: none"> <li>In grey matter, MD and metabolite ratios measured on day 1 were predictive of values on day 3</li> <li>In white matter, MD, FA and (NAA)/choline on days 1 and 3 were strongly related</li> <li>Hypothermia appeared to attenuate the severity and progression of brain injury in the six treated newborns</li> </ul>             |
| Weird <i>et al</i> <sup>89</sup>   | <ul style="list-style-type: none"> <li>Born at 36 weeks GA or after</li> <li>Abnormal tone patterns</li> <li>Feeding difficulties</li> <li>Altered alertness</li> <li>At least 3 of (1) late decelerations on fetal monitoring or meconium staining</li> <li>Delayed onset of respiration, (2) pH &lt;7.1, (4) Apgar scores &lt;7 at 5 min or (5) multorgan failure</li> </ul> | HIE and healthy term        | Within 3 weeks | 207                      | ADC, FA, RA                       | <ul style="list-style-type: none"> <li>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)</li> <li>WM also graded normal, moderate or severe</li> </ul> | –  | ROI: CS (central), BGT, lateral lentiform nuclei, medial thalamus, ventrolateral nuclei of thalamus, PLIC, brainstem, cerebellum   | <ul style="list-style-type: none"> <li>During the first week, FA values were decreased with both severe and moderate WM and BGT injury, whereas ADC values were reduced only in severe WM injury and some severe BGT injury</li> <li>Abnormal ADC values pseudonormalised during the second week, whereas FA values continued to decrease</li> </ul>                     |

Continued

Table 1 Continued

| Authors                             | Definition/criteria   | Groups   | Age at scan                                       | n=Neonates with DWI scan | Metrics                | Conventional MRI findings/scoring criteria  | Outcomes   | Whole brain/ROI  | Reported findings  |
|-------------------------------------|---|--|---|--------------------------|------------------------|---|--|--|--|
| van Pul <i>et al</i> <sup>20</sup>  | Clinical symptoms of NE present in first days of life together with two or more of fetal heart rate abnormalities, umbilical artery pH less than 7.10, meconium stained fluid, Apgar score after 5 min of less than 7                                     | HIE  | Within 10 days                                    | 22                       | ADC, FA, AD            | - 11 neonates had focal white matter injury   | Follow-up MRI at 3 m:<br>In six infants (severe) tissue loss or signal intensity abnormalities observed in the region of lesion, with abnormalities in the basal ganglia in 2, and mildly to moderately delayed myelination in four and normal myelination in 2. In both infants without abnormalities in the region of the infarct, myelination was delayed | ROI: CC and WM   | 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 indexes<br>The relative change in anisotropy decreased linearly with time, with the strongest trend in anisotropy index AD  |
| AlAmrani <i>et al</i> <sup>21</sup> | Born at 36 weeks GA or after Evidence of fetal distress, for example, history of acute perinatal event, cord pH $\leq 7.0$ or base deficit $\leq 16$ , or continued need for ventilation initiated at birth for at least 10 min<br>Moderate or severe HIE | Cooled HIE<br>Newborn NE and 6 months NE               | 10 days   | 29                       | ADC, FA                | Barkovich scoring—0 for 'no brain injury', 1 for 'basal ganglia injury pattern', 2 for 'watershed injury pattern', and 3 to 4 for 'near-total injury pattern'   | Adverse outcomes: cerebral palsy, global developmental delay, epilepsy<br>In neonates who developed an adverse outcome, ADC values significantly decreased on days 2-3 of life in the thalamus, PLIC and lentiform nuclei<br>Then, ADC values increased (pseudonormalisation) and FA decreased around day 10 in the same ROIs                                | ROI: thalamus, PLIC, lentiform nucleus, front and post WM, cortical GM   | 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 the lentiform nucleus<br>FA values decreased in the same regions around day 30 of life<br>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  |
| Kansagra <i>et al</i> <sup>22</sup> | Born at 36 weeks GA or after<br>Moderate or severe HIE<br>Apgar score less than 5 within 10 min of birth, prolonged resuscitation at birth, pH less than 7.0 within 60 min of birth or base deficit greater than 12                                       | Newborn NE and 6 months NE                             | 0 months and 6 months (excluded from this review) | 12                       | FA, MD, OD, FW (NODDI) | -<br>Infants assigned a validated neuromotor score: 0 for normal development, 1 for abnormal tone or reflexes, 2 for abnormal deficit of power, 4 for cranial nerve involvement with motor abnormality and 5 for spastic quadriplegia<br>All infants had scores of 0 or one at an average 318 days        | Infants assigned a validated neuromotor score: 0 for normal development, 1 for abnormal tone or reflexes, 2 for abnormal deficit of power, 4 for cranial nerve involvement with motor abnormality and 5 for spastic quadriplegia<br>All infants had scores of 0 or one at an average 318 days  | ROI - PLIC, ALIC, OR, CCgenu, CCsplen                                    | At birth, the CC collectively demonstrated significantly higher FA than the ALIC or OR<br>Moreover, the CC demonstrated significantly lower OD and higher FW than the PLIC, ALIC or optic radiations at birth<br>Measured FA was significantly higher white matter tracts. In contrast, MD was significantly higher only within the PLIC, ALIC OR and splenium. OD was significantly higher only within the ALIC and OR<br>Measured FW was significantly lower at 6 m than at birth in the OR, genu and splenium |
| Lee <i>et al</i> <sup>23</sup>      | Retrospective diagnosis of NE, all cooled   | NE (normal MRI) and healthy preterm at term equivalent | 5-18 days   | 12/24/12                 | ADC, FA                | 11 had predominantly BGT injury without WM injury<br>Four had predominantly diffuse cortical injuries with underlying WM but no deep GM changes<br>Six had only WM injuries in the watershed distribution<br>Three had global mixed GM and WM injuries<br>12 of these neonates also had CC signal changes | Normal development observed in 2 children at 1Y, and in 1 at 6Y  | ROI: PLIC, temporal, occipital, parietal and frontal WM, CCgenu, CCsplen | We found significant reductions in measured FA in white matter in the ANE neonates compared with the control group<br>There were, however, no significant differences in measured FA in white matter between the NIE and the control group<br>The FA of CCgen and CCsplen was the lowest in the global pattern, followed by the cortical pattern, the watershed pattern and the basal ganglia pattern  |

ADC, apparent diffusion coefficient; ALIC, anterior limb of the internal capsule; ANE, anencephalic; neonate with an abnormal MRI; BGT, basal ganglia/thalamus; BSID, Bayley Scale of Infant Development; CC, corpus callosum; CST, corticospinal tract; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FW, free water fraction; GMD3, Griffiths Mental Development Scales; GMFCS, Gross Motor Function Classification System; HIE, hypoxic-ischaemic encephalopathy; IFOF, inferior fronto-occipital fasciculus; MAP, mean arterial blood pressure; NE, neonatal encephalopathy; NICU, neonatal intensive care unit; NINMS, NICU network neurobehavioral scale; OR, optic radiations; PCA, postconceptional age; PLIC, posterior limb of the internal capsule; ROI, regions of interest; SFT, superior longitudinal fasciculus; TBS3, 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)

| Region of Interest (ROI)         | n=ROI mentioned in results |
|----------------------------------|----------------------------|
| PLIC                             | 13                         |
| CCGenu                           | 13                         |
| CCSplen                          | 13                         |
| ALIC                             | 5                          |
| Cing., IFOF/ILF, CerebralP       | 4                          |
| CCBody, SLF                      | 3                          |
| CR, Fornix, OR, CerebellarP, CST | 2                          |
| EC                               | 1                          |
| Global WM                        | 4                          |

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 (NNS) and one clinical test applicable only to those neonates who developed cerebral palsy; Gross Motor Function Classification System (see [table 3](#)).<sup>17–19 23 25–27</sup> The remaining four studies described other clinical tests including measurements of neuronal metabolism, follow-up MRI scans and other arbitrary scoring systems.<sup>28 30–32</sup> Six of these studies were able to show an association between adverse outcomes and FA measurements in the PLIC and CC.<sup>18 23 25–27 31</sup> 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, NNS (total motor score), BSID (psycho-motor developmental index) and global developmental

**Table 3** A summarising table of clinical assessments used to assess outcomes

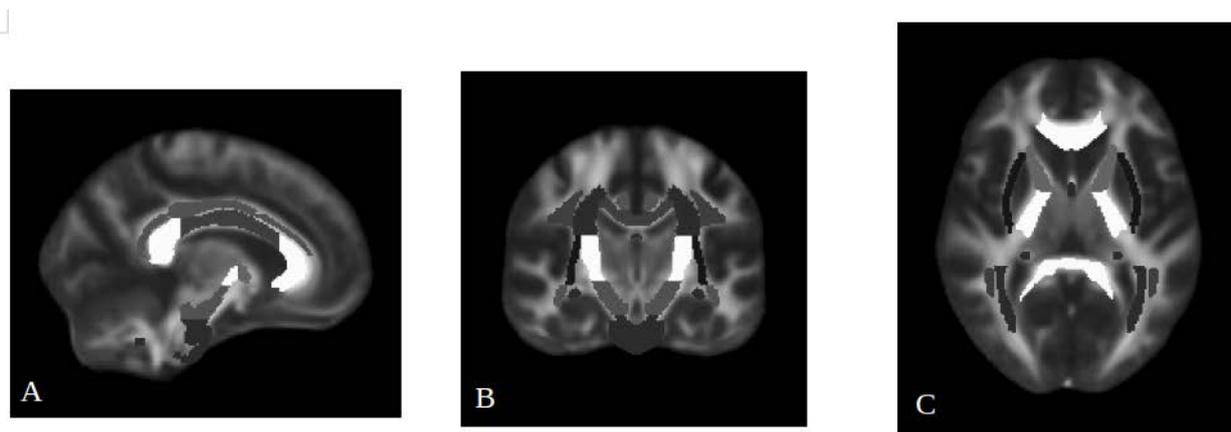
| Clinical assessment | n=Included in outcomes |
|---------------------|------------------------|
| GMDS                | 4                      |
| BSID                | 3                      |
| GMFCS               | 2                      |
| NBNA                | 1                      |
| NNNS                | 1                      |

BSID, Bayley Scales of Infant Development; GMDS, Griffiths Mental Development Scales; GMFCS, Gross Motor Function Classification System; NBNA, Neonatal Behavioural Neurological Assessment; NNS, NICU Network Neurobehavioural Scale.

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<sup>6</sup> 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,<sup>6</sup> Rutherford<sup>34</sup> 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.<sup>17 18 21 22 29</sup>

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.<sup>7</sup> 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<sup>35</sup> and even motor<sup>36</sup> 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.<sup>37</sup>

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.<sup>38</sup> DWI is the most sensitive MRI sequence for imaging the encephalopathy 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.<sup>39 40</sup> 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.<sup>41</sup> 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.

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