Tractography of white-matter tracts in very preterm infants: a 2-year follow-up study

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ABBREVIATIONS
ADC Apparent diffusion coefficient
BSID-III Bayley Scales of Infant Development (version 3)
DTI Diffusion tensor imaging
PLIC Posterior limb of the internal capsule

White-matter injury is a common finding on magnetic resonance imaging (MRI) performed around term-equivalent age in very preterm infants.1–5 It may eventually result in damage, underdevelopment, and atrophy of the internal capsule and the corpus callosum.6–9 Recently it has been demonstrated that fibre tractography offers additional insight into the developmental status of white matter by visualization and characterization of white-matter tracts.10–15 Moreover, diffusion tensor imaging (DTI) has been proposed as an additional tool to provide more adequate prognostic information, around term-equivalent age in relation to cognitive and psychomotor neurodevelopmental outcome, than conventional MRI in preterm and low-birth-weight infants.16–20

Although these studies clearly indicate the potential of DTI to predict neurodevelopmental damage at a later age, its independent value is not well established; well-known individual predictors of neurodevelopmental outcome, such as gestational age, sex, perinatal infections, oxygen requirement, and mechanical ventilation dependency, intrauterine growth restriction, and white-matter injury and ventricular dilation on MRI, were not taken into consideration in most studies. Previously, we demonstrated in very preterm infants around term-equivalent age that, in particular, the white-matter tracts passing through the posterior limb of the internal capsule (PLIC) or through the corpus callosum are associated with developmental status at term-equivalent age, independent of the degree of preterm birth and the classification of white-matter injury.13 The aim of the present study was to establish the independent predictive value of DTI tractography performed around term-equivalent age, especially of fibres passing through the PLIC and corpus callosum, on neurodevelopmental outcome at the age of 2 years.

AIM The aim of this study was to determine whether tractography of white-matter tracts can independently predict neurodevelopmental outcome in very preterm infants.

METHOD Out of 84 very preterm infants admitted to a neonatal intensive care unit, 64 (41 males, 23 females; median gestational age 29.1 weeks [range 25.6–31.9]; birthweight 1163g [range 585–1960]) underwent follow-up at 2 years. Diffusion tensor imaging (DTI) values obtained around term were associated with a neurological examination and mental and psychomotor developmental index scores at 2 years based on the Bayley Scales of Infant Development (version 3). Univariate and logistic regression analyses tested for associations between DTI values and follow-up parameters. Cut-off values predicting motor delay and cerebral palsy (CP) were determined for fractional anisotropy, apparent diffusion coefficient (ADC), and fibre lengths.

RESULTS Infants with psychomotor delay and CP had significantly lower fractional anisotropy values ($p=0.002$, $p=0.04$ respectively) and shorter fibre lengths ($p=0.02$, $p=0.02$ respectively) of the posterior limb of the internal capsule. Infants with psychomotor delay also had significantly higher ADC values ($p=0.03$) and shorter fibre lengths ($p=0.002$) of the callosal splenium. Fractional anisotropy values of the posterior limb of the internal capsule independently predicted motor delay and CP, with sensitivity between 80 and 100% and specificity between 66 and 69%. ADC values of the splenium independently predicted motor delay with sensitivity of 100% and specificity of 65%.

INTERPRETATION Diffusion tensor imaging tractography at term-equivalent age independently predicts psychomotor delay at 2 years of age in preterm infants.
METHOD

Preterm infants

As part of a continuing prospective neuroimaging study of very preterm infants (gestational age <32wks) admitted to the neonatal intensive care unit of the Leiden University Medical Centre between May 2006 and October 2007, 113 infants underwent MRI. MRI was performed at a median postmenstrual age of 43.4 weeks (range of 40–62wks). Ethical approval for the study was given by the University’s institutional review board and informed parental consent was obtained for each infant. DTI was performed in 102 infants. Three infants with congenital brain abnormalities were excluded. In 15 additional infants, fibre tractography was not possible owing to motion artefacts. In the remaining 84 infants, a complete DTI dataset was acquired. Clinical parameters were collected from the patients’ files. Baseline characteristics and baseline DTI parameters of the entire cohort have been published previously.5

Image and data acquisition

All MRI examinations were performed on a 3T MR system (Philips Medical Systems, Best, the Netherlands) according to a standardized protocol.22 The infants were sedated using chloral hydrate (55mg/kg), lay supine, and were swaddled during the imaging procedure. Ear protection consisted of neonatal earmuffs (Natus Mini Muffs; Natus Medical, San Carlos, CA, USA) covered by a headphone. The MRI examination included a DTI sequence (spin-echo echo planar imaging, repeat time 7456ms, echo time 54ms, slice thickness 2mm, gap 0mm, voxel size 1.4mm × 1.4mm × 2mm; with diffusion acquisitions in 32 directions and a b value of 1000s/mm², echo planar imaging factor 56) with an image time of 5 minutes 34 seconds.

White-matter injury and ventricular dilation

To assess white-matter injury and ventricular dilation, all T1-, T2-, and T2*-weighted gradient-echo sequences were analysed by two investigators (FTdB and LML or SJS) together by consensus. The presence and location of more than six punctate white-matter lesions and/or cystic and/or haemorrhagic white-matter lesions were scored5 as well as the level of myelination of the PLIC compared with the lentiform nucleus. Punctate white-matter lesions were defined respectively as punctate high and low SI lesions, more pronounced on T1- than on T2-weighted images, not visible on T2*-weighted gradient echo sequences.23–25 Cystic white-matter lesions were scored on T1- and T2-weighted sequences, whereas haemorrhagic lesions were scored on T2*-weighted gradient-echo sequences. On coronal reconstructions from the three-dimensional T1-weighted images, the ventricular index was measured as the total width of the lateral ventricles, divided by 2, analogous to ventricular index measurements on ultrasound. A ventricular index between 12 and 16mm was considered moderate dilation, and a ventricular index larger than 16mm was considered severe dilation.5

Follow-up

At around 2 years’ corrected age, infants were seen for clinical follow-up by an experienced neonatologist, unaware of the MRI findings. Each child underwent a standardized neurological examination to assess the presence of cerebral palsy (CP) or abnormal muscular tone. In all infants, a Gross Motor Function Classification System (GMFCS) level was assigned.26 Because of the great difference between GMFCS level I and level V, level I was not included. Therefore, an infant with at GMFCS level of II or above was considered to have CP.

Cognitive and psychomotor development was assessed using the Dutch version of the Bayley Scales of Infant Development, version 3 (BSID-III). A mental developmental index

What this paper adds

• DTI values obtained around term-equivalent age can predict neurodevelopmental outcome in very preterm infants.
• DTI in very preterm infants may be considered as an independent predictor of neurodevelopment.
score and a psychomotor developmental index score were calculated for the corrected age of the child. A score of one standard deviation or more below the normative mean was defined as a delay in development. Three infants, diagnosed with CP, in whom testing of the gross and fine motor function with the BSID-III was not feasible, were assigned a psychomotor developmental index score of 50.

To evaluate child behaviour, the Dutch version of the Child Behavior Checklist was sent to the child’s address before the follow-up visit, to be completed by either parent. The questionnaire consists of 99 items rated on a three-point scale. By summing the scores, an internalizing, externalizing, total, and other problem score can be computed. Dichotomized T scores between the 84th and 90th centiles were assigned in the borderline range, whereas T scores above 90th centile were assigned in the abnormal range and defined as behavioural problems.

Statistical analysis
We analysed data with SPSS version 18.0 for Windows (SPSS Inc, Chicago, IL USA). Continuous variables were expressed as mean with standard deviation and range, and categorical variables as count with percentage. DTI parameters of infants with and without neurodevelopmental delay (BSID-III), CP, and behavioural problems (Child Behavior Checklist) were compared using a Student’s t-test or Mann-Whitney U test where appropriate. Mean differences were reported.

Backward logistic regression was used to adjust for potentially confounding clinical and MRI parameters related to outcome and/or DTI parameters. Subsequently, using MedCalc version 11.6 for Windows (MedCalc Software, Mariakerke, Belgium), receiver operating characteristic curves and corresponding areas under the curve were generated for the DTI parameters that were independent predictors for neurodevelopmental outcome according to logistic regression. Cut-off values and predictive accuracy of these individual DTI parameters were assessed.

Two-sided tests were used throughout and a p value of <0.05 was considered statistically significant.

RESULTS
Follow-up
Follow-up was obtained in 64 of the 84 (76.2%) infants. Mean age at follow-up was 31 months (SD 4.4, range 23–44).

Twenty infants were lost to follow-up for miscellaneous reasons such as declining to participate or practical problems, including travel distance to the hospital. At term-equivalent age there were no differences in clinical or DTI parameters between infants with or without follow-up.
Gestational age
Female 23 (35.9)
Male 41 (64.1)

Posterior limb of the internal capsule
Diffusion tensor imaging values Mean (SD)
Haemorrhagic lesions 3 (4.7)
Cysts 4 (6.3)
Severe ventricular dilation 12 (18.8)
More than six punctate white-matter lesions 11 (17.2)

Weight at MRI (g) 4010 (2010–6200)

Continuous clinical parameters Median (range)
Birthweight 1163 (585–1960)
Intrauterine growth restriction 8 (12.5)

White-matter injury n (%)
More than six punctate white-matter lesions 11 (17.2)
Moderate ventricular dilation 35 (54.7)
Severe ventricular dilation 12 (18.8)
Cysts 4 (6.3)
Haemorrhagic lesions 3 (4.7)

Diffusion tensor imaging values Mean (SD)
Fractional anisotropy of the PLIC in infants without and with motor delay was significantly lower in infants with CP compared to those without CP (p<0.001). The plot in Fig. S2 (online supporting information) shows the fractional anisotropy of the PLIC in infants without and with motor delay.

We found a significant relation between myelination of the PLIC and fractional anisotropy (p<0.001) and ADC (p<0.001) of the PLIC. All infants with psychomotor delay according to the BSID-III and CP according to the GMFCS showed incomplete myelination of the PLIC; however, this finding was not significant as, respectively, 77.6% and 79.3% of the infants without psychomotor delay or CP also showed an incompletely myelinated PLIC. Therefore (incomplete) myelination in the PLIC was not directly related to outcome (p=0.57, both for psychomotor delay and for CP).

Clinical parameters, white-matter injury, and DTI parameters
The baseline clinical and DTI parameters in this cohort (n=64) are shown in Table I. Median gestational age was 29.1 weeks (range 25.6–31.9); 41 infants were male, 23 female. Table I also shows the number and percentage of infants with white-matter injury, consisting of more than six punctate white-matter lesions and moderate and severe ventricular dilation. The location of the punctate white-matter lesions was mainly in the periventricular white matter of the centrum semi ovale, at the level of the trigonum or optic radiation. There were only a few infants with cystic and/or haemorrhagic lesions.

Table II shows the mean differences in baseline DTI parameters between infants with normal development and those with abnormal cognitive development, abnormal motor development, or presence of CP after 2 years. Three infants (3.6%) showed cognitive delay and 5 (6.0%) had psychomotor delay according to the BSID-III. According to the GMFCS, 5 (6.0%) infants had CP.

Infants with psychomotor delay according to the BSID had significantly lower fractional anisotropy values and shorter fibre lengths of the PLIC (p=0.002 and p=0.02 respectively), and higher ADC values and shorter fibre lengths of the callosal splenium (p=0.03 and p=0.002 respectively). Infants with CP according to the GMFCS also had significantly lower fractional anisotropy values and shorter fibre lengths of the PLIC (p=0.04 and p=0.02). The plot in Fig. S2 (online supporting information) shows the fractional anisotropy of the PLIC in infants without and with motor delay.

We found a significant relation between myelination of the PLIC and fractional anisotropy (p<0.001) and ADC (p<0.001) of the PLIC. All infants with psychomotor delay according to the BSID-III and CP according to the GMFCS showed incomplete myelination of the PLIC; however, this finding was not significant as, respectively, 77.6% and 79.3% of the infants without psychomotor delay or CP also showed an incompletely myelinated PLIC. Therefore (incomplete) myelination in the PLIC was not directly related to outcome (p=0.57, both for psychomotor delay and for CP).

Table I: Distribution of categorical clinical parameters, continuous clinical parameters, white-matter injury, and diffusion tensor imaging parameters

<table>
<thead>
<tr>
<th>Categorical clinical parameter</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Male</td>
<td>41 (64.1)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Gestational age ≥28wk</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Birthweight ≥1000g</td>
<td>21 (32.8)</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>8 (12.5)</td>
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<table>
<thead>
<tr>
<th>Continuous clinical parameters</th>
<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>29.1 (25.6–31.9)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1163 (585–1960)</td>
</tr>
<tr>
<td>Weight at MRI (g)</td>
<td>4010 (2010–7005)</td>
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<tr>
<th>White-matter injury n (%)</th>
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<tbody>
<tr>
<td>More than six punctate white-matter lesions</td>
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<tr>
<td>Moderate ventricular dilation</td>
</tr>
<tr>
<td>Severe ventricular dilation</td>
</tr>
<tr>
<td>Cysts</td>
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<tr>
<td>Haemorrhagic lesions</td>
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<tr>
<th>Diffusion tensor imaging values</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Posterior limb of the internal capsule</td>
<td></td>
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<tr>
<td>Fractional anisotropy</td>
<td>0.37 (0.02)</td>
</tr>
<tr>
<td>ADC (10⁻³mm²/s)</td>
<td>1.06 (0.05)</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>58.7 (7.8)</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td></td>
</tr>
<tr>
<td>CCA fractional anisotropy</td>
<td>0.37 (0.04)</td>
</tr>
<tr>
<td>CCA ADC (10⁻³mm²/s)</td>
<td>1.32 (0.10)</td>
</tr>
<tr>
<td>CCA length (mm)</td>
<td>46.9 (10.5)</td>
</tr>
<tr>
<td>CCP fractional anisotropy</td>
<td>0.40 (0.04)</td>
</tr>
<tr>
<td>CCP ADC (10⁻³mm²/s)</td>
<td>1.36 (0.12)</td>
</tr>
<tr>
<td>CCP length (mm)</td>
<td>58.7 (12.8)</td>
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<td>The baseline clinical and DTI parameters in this cohort (n=64) are shown in Table I. Median gestational age was 29.1 weeks (range 25.6–31.9); 41 infants were male, 23 female. Table I also shows the number and percentage of infants with white-matter injury, consisting of more than six punctate white-matter lesions and moderate and severe ventricular dilation. The location of the punctate white-matter lesions was mainly in the periventricular white matter of the centrum semi ovale, at the level of the trigonum or optic radiation. There were only a few infants with cystic and/or haemorrhagic lesions.</td>
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| Table II: Mean difference [95% confidence interval] in diffusion tensor imaging (DTI) parameters of the posterior limb of the internal capsule (PLIC) and corpus callosum (CC) for neurodevelopmental outcome (BSID-III, GMFCS) in 64 infants |
|-------------------------------------------------|------------------|------------------|------------------|
| DTI parameters                                  | Normal development vs mental delay (BSID-III, n=3) p  | Normal development vs psychomotor delay (BSID-III, n=5) p  | Normal development vs cerebral palsy (GMFCS), n=5 p |
| PLIC parameters                                 | Fractional anisotropy 0.027 (−0.016 to 0.070) 0.05 | 0.027 (0.013 to 0.041) 0.002 a | 0.020 (0.004 to 0.040) 0.04 a |
|                                                | ADC 0.013 (−0.047 to 0.072) 0.81 | −0.020 (−0.059 to 0.018) 0.28 | −0.004 (−0.049 to 0.042) 0.90 |
|                                                | Length 5.76 (3.78 to 15.30) 0.18 | 7.90 (4.10 to 11.70) 0.02 a | 7.39 (2.99 to 11.79) 0.02 a |
| CC parameters                                   | CCA fractional anisotropy 0.021 (−0.030 to 0.073) 0.45 | −0.002 (−0.046 to 0.041) 0.66 | 0.0007 (−0.041 to 0.042) 0.53 |
|                                                | CCA ADC 0.005 (−0.112 to 0.121) 0.79 | −0.034 (−0.125 to 0.056) 0.40 | −0.016 (−0.110 to 0.078) 0.77 |
|                                                | CCA length −0.224 (−12.84 to 12.39) 0.89 | 6.29 (−3.33 to 15.91) 0.19 | 1.55 (−8.29 to 11.39) 0.87 |
|                                                | CCP fractional anisotropy −0.007 (−0.036 to 0.049) 0.96 | 0.001 (−0.032 to 0.035) 0.95 | −0.006 (−0.039 to 0.028) 0.70 |
|                                                | CCP ADC −0.058 (−0.202 to 0.086) 0.58 | −0.148 (−0.250 to −0.045) 0.03 a | −0.086 (−0.194 to 0.023) 0.07 |
|                                                | CCP length 2.61 (12.90 to 18.11) 0.62 | 19.32 (8.23 to 30.42) 0.002 a | 13.06 (−6.13 to 32.26) 0.05 |

*Statistically significant: BSID-III, Bayley Scales of Infant Development, version 3; GMFCS, Gross Motor Function Classification System; ADC, apparent diffusion coefficient; CCA, genu of the corpus callosum; CCP, splenium of the corpus callosum.
We found no correlation between DTI parameters at term-equivalent age and behavioural problems based on Child Behavior Checklist scores after 2 years.

Backward logistic regression analyses, correcting for potentially confounding clinical parameters (gestational age, sex, intrauterine growth restriction, perinatal infections, number of days of oxygen requirement, number of days of mechanical ventilation), white-matter injury, and ventricular dilation on MRI, showed that a lower fractional anisotropy value and a shorter fibre length of the PLIC were independent predictors for psychomotor delay ($p=0.004$; odds ratio $0.27$ [95% CI 0.09–0.80] and $p=0.001$, odds ratio $0.99$ [95% CI 0.98–0.99]) and fractional anisotropy of the PLIC also to a lesser extent for CP ($p=0.09$; odds ratio $0.46$ [95% CI 0.21–1.03]). A higher ADC value of the callosal splenium ($p=0.02$; odds ratio $1.11$ [95% CI 1.02–1.21]) was an independent predictor for psychomotor delay.

Table III shows the summary statistics of the receiver operating characteristic curves for the relevant DTI parameters predicting motor delay and CP. Because DTI values are age dependent, receiver operating characteristic curves were only based on 59 infants imaged at term-equivalent age (between 40 and 44 weeks). Follow-up was available in 44 out of 59 (74.6%) infants.

A cut-off value of the fractional anisotropy in the PLIC of 0.36 predicted motor delay with a sensitivity of 100% and a specificity of 69% (Fig. S3, online supporting information) and CP with a sensitivity of 80% and a specificity of 66%. A fibre length shorter than 53.9mm through the PLIC predicted motor delay with a sensitivity of 80% and a corresponding specificity of 79%.

A cut-off value for the ADC of the callosal splenium of $1.38 \times 10^{-3}$ mm$^2$/s predicted motor delay with a sensitivity of 100% and a specificity of 65%.

**DISCUSSION**

In this study we correlated DTI values of white-matter tracts acquired around term-equivalent age in very preterm infants with neurodevelopmental follow-up at the age of 2 years. Low fractional anisotropy values and decreased fibre lengths of the PLIC at term-equivalent age are associated with psychomotor delay and CP, and high ADC values and short fibre lengths of the callosal splenium with psychomotor delay.

These associations were independent from other types of brain damage at term-equivalent age such as white-matter injury, ventricular dilation, and/or clinical parameters, and can predict motor delay and/or CP with a high sensitivity and reasonable specificity.

The main pathogenic mechanisms for white-matter injury in the very preterm neonate are ischemia and infection. These often co-exist and may lead to focal or diffuse white-matter injury and/or haemorrhages in the perinatal period owing to the vulnerability of the developing white matter, immature vasculature, and impaired cerebrovascular auto-regulation of the immature brain. DTI studies have suggested axonal loss in the white matter of preterm infants at term-equivalent age and have been shown to be predictive for neurodevelopmental outcome.

Our data partly confirm the results of the study by Arzoumanian et al. showing a correlation between a decreased fractional anisotropy of the PLIC near term-equivalent age in low-birthweight preterm infants and infants with neurological impairments, including CP at the age of 18 and 24 months. Also, our data substantiate the findings of Rose et al. in which a reduction in fractional anisotropy and higher ADC values in the callosal splenium and right-sided PLIC at term-equivalent age were correlated with abnormal neurological outcome at 18 months. In our study, we corrected for all clinical and MRI factors separately in one regression model, whereas Rose et al. used one overall MRI score. Van Kooij et al. demonstrated in a recent study that tract-based spatial statistics of fractional anisotropy and axial and radial diffusivity of DTI data at term-equivalent age are a potential biomarker for subsequent neurodevelopment. After correction for gestational age and postmenstrual age at imaging, gross motor scores were associated with radial diffusivity in the corpus callosum and internal and external capsule. In an earlier fibre tractography study, van Kooij et al. found sex differences for associations between fibre-tracking parameters and cognitive and motor outcome at 2 years of age in preterm infants after correcting for gestational age, birthweight, intraventricular haemorrhage, white-matter injury, and maternal education. In our study we did not find sex differences, but our data show that lower fractional anisotropy values of the PLIC, shorter fibre lengths of the PLIC, and higher ADC values of the callosal splenium, Table III: Summary statistics of receiver operating characteristic curves for fractional anisotropy and length of the posterior limb of the internal capsule (PLIC) and apparent diffusion coefficient (ADC) of the splenium

<table>
<thead>
<tr>
<th>Area under the curve ($p$)</th>
<th>Cut-off value</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional anisotropy of the PLIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor delay</td>
<td>0.89 (0.001)</td>
<td>0.36</td>
<td>100 (48–100)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>0.79 (0.001)</td>
<td>0.36</td>
<td>80 (28–100)</td>
</tr>
<tr>
<td>Length of the PLIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor delay</td>
<td>0.80 (0.03)</td>
<td>53.9</td>
<td>80 (28–100)</td>
</tr>
<tr>
<td>ADC of the splenium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor delay</td>
<td>0.80 (0.001)</td>
<td>1.38</td>
<td>100 (48–100)</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval.
after correcting for clinical parameters, white-matter injury, and ventricular dilation, are independent predictors for psychomotor delay and/or CP at the age of 2 years.

The predictive value of MRI findings for motor and cognitive development in preterm infants is an area of ongoing research. Prediction of neurodevelopmental outcome in infants born very preterm is considered to be highly important, as early intervention may be beneficial for neurodevelopmental outcome. So far, most studies have used qualitative assessment of white-matter injury combined with ventricular dilation or delay in myelination to predict neurodevelopmental outcome. In a study by Woodward et al. qualitative assessment of white-matter injury showed reasonable sensitivity (65%) and specificity (85%) to predict motor delay. Spittle et al. demonstrated that white-matter abnormalities predicted a delay in motor development at 12 months’ corrected age with a specificity of more than 90%; however, the sensitivity was very low. Qualitative assessment of diffuse high-signal intensity of the white matter in itself did not correlate with abnormal neurodevelopmental outcome at 2 years, whereas ventricular dilation and the existence of more than six punctate white-matter lesions did. By generating receiver operating characteristic curves, we determined cut-off values for the fractional anisotropy of the PLIC, the fibre length of the PLIC, and the ADC value of the splenium of the corpus callosum, predicting motor delay with a high sensitivity and reasonable specificity.

A limitation of our study is that follow-up was unavailable in 20 out of 84 (23.8%) of the very preterm infants. While it could be argued that inclusion bias affected our data, at term-equivalent age there were no differences in clinical parameters, white-matter injury, or DTI values between infants with and without follow-up. In addition, the low number of infants with an unfavourable outcome reduces the statistical power of the study. Although our results show that DTI fibre tracking of the PLIC and corpus callosum around term-equivalent age offers valuable data to assess an individual prognosis after 2 years, it should be kept in mind that combining conventional MRI with quantitative MRI techniques improves the performance of MRI for prognostication. The set-up of our study with relatively short-term follow-up at 2 years of age limits confident prognosis, especially for cognitive impairment. Long-term follow-up at school age is needed to evaluate further the prognostic values of certain MRI findings and quantitative values around term-equivalent age for cognitive neurodevelopmental outcome.

We conclude that DTI tractography values obtained around term-equivalent age are of additional help in predicting neurodevelopmental outcome at 2 years’ corrected age in infants born very preterm. Prediction of motor delay and CP is possible by determining the fractional anisotropy value and fibre length of the PLIC and the ADC value of the splenium of the corpus callosum.

ACKNOWLEDGEMENTS

LM Leijser was financially supported by ZonMw, the Netherlands Organization for Health Research and Development (grant number 920-03-388) for collecting data on very preterm infants. We acknowledge Andrea van Steenis who helped to collect the DTI values, and Wouter Teeuwisse for technical assistance.

SUPPORTING INFORMATION
The following additional material may be found online:

Figure S1: (a) Axial colour-coded diffusion tensor imaging (DTI) map with right (→) and left (←) posterior limb of the internal capsule (PLIC) in blue. (b) Sagittal colour-coded DTI map with corpus callosum in red, the regions of interest of genu (→) and splenium (←) are defined. The ‘x’ marks the place where a single seed point was placed to generate the fibre tracts.

Figure S2: Fractional anisotropy of the posterior limb of the internal capsule in children with and without motor delay.

Figure S3: Receiver operating characteristic curve for motor delay of the fractional anisotropy of the posterior limb of the internal capsule.

REFERENCES

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