

# Does Diffusion Tensor Imaging-Based Tractography at 3 Months of Age Contribute to the Prediction of Motor Outcome After Perinatal Arterial Ischemic Stroke?

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**Background and Purpose**—After perinatal arterial ischemic stroke, diffusion-weighted imaging (DWI) and early evaluation of spontaneous motor behavior can be used to predict the development of unilateral motor deficits. The aim of this study was to investigate whether diffusion tensor imaging-based tractography at 3 months of age contributes to this prediction.

**Methods**—Twenty-two infants with unilateral perinatal arterial ischemic stroke were included and scanned during the neonatal period. DWI was used to assess restricted diffusion in the cerebral peduncle. At the age of 3 months, diffusion tensor imaging-based tractography of the corticospinal tracts was performed along with assessment of the movement repertoire. The role of DWI, diffusion tensor imaging, and motor assessment in predicting unilateral motor deficits were compared by calculating the positive and negative predictive values for each assessment.

**Results**—Eleven infants (50%) showed abnormal motor behavior at 3 months with subsequent development of unilateral motor deficits in 8 as determined at follow-up (9–48 months, positive predictive value 73%). Diffusion tensor imaging-based tractography correctly predicted the development of unilateral motor deficits in all 8 infants (positive predictive value 100%). A diagnostic neonatal DWI was available in 20 of 22 (91%) infants. Seven infants showed an abnormal DWI, resulting in unilateral motor deficits in 6 infants (positive predictive value 86%). All assessments had a negative predictive value of 100%.

**Conclusions**—Diffusion tensor imaging-based tractography at 3 months can be used to predict neurodevelopmental outcome after perinatal arterial ischemic stroke. It has a similar predictive value as DWI in the neonatal period and can especially be of additional value in case of an indecisive neonatal DWI or unexpected abnormal early motor development. (*Stroke*. 2011;42:3410-3414.)

**Key Words:** cerebral palsy ■ diffusion tensor imaging ■ diffusion tensor tractography ■ diffusion-weighted imaging ■ perinatal brain damage

Perinatal arterial ischemic stroke (PAIS) occurs with an estimated incidence of 1:2300 live births.<sup>1</sup> With the development of motor deficits in 30% to 60% of all cases, healthcare costs during the neonatal period and beyond are enormous.<sup>2</sup> Treatment options for the acute phase are still limited to supportive measures.<sup>1</sup> Several therapies have shown positive results in animal models, but few have been tested in newborn stroke. The introduction of new therapies for clinical use would require a careful selection of eligible patients. Assessment of the extent of brain injury and the expected adverse neurological sequelae are therefore essential.

After PAIS, conventional MRI, especially diffusion-weighted imaging (DWI),<sup>3–5</sup> can be used to detect ischemic tissue and to

predict motor outcome.<sup>2–5</sup> The observed restricted diffusion in the cerebral peduncle is predictive of Wallerian degeneration and subsequent unilateral motor deficits (UMD) and is therefore also referred to as “pre-Wallerian degeneration.”<sup>3–5</sup>

Diffusion tensor imaging (DTI) allows in vivo observation of the microstructural and architectural properties of the white matter.<sup>6,7</sup> Infants with perinatal brain injury who did develop UMD often show abnormalities in DTI parameters in later childhood.<sup>8,9</sup> Most of these studies, however, included children who were already diagnosed to have UMD.

The aim of this study was to investigate whether DTI-based tractography of the corticospinal tracts (CSTs) at the age of 3 months after PAIS is predictive for the development of UMD. Furthermore, we aim to study whether this provides

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additional information compared with the already acquired DWI data in the neonatal period and assessment of motor behavior at 3 months of age.

## Methods

### Patient Population

Infants with a unilateral PAIS born between 2006 and 2010 who had an MRI in the neonatal period and again at the age of 3 months were eligible for inclusion in this study. Infants were included if neurodevelopmental follow-up was available beyond the age of 12 months or if overt signs of developing UMD were already observed before this age. Scans were acquired as part of standard clinical work-up in infants suspected of PAIS.

### Magnetic Resonance Imaging

All scans were acquired on a 1.5-Tesla Philips Gyroscan (Philips Medical Systems, Best, the Netherlands). Infants were sedated with a combination of chlorpromazine (0.5 mg/kg), pethidine (2 mg/kg), and promethazine (0.5 mg/kg) intramuscularly. A vacuum pillow (Med-Tec, Orange City, IA) was used to prevent movement of the head. Minimuffs (Natus Medical Inc, San Carlos, CA) were used for hearing protection. Heart rate and transcutaneous oxygen saturation were monitored by pulse oximetry (Nonin, Minneapolis, MN) as well as respiration rate (Philips ACS-NT, Best, the Netherlands).

To acquire the neonatal DWI data, we used an axial single-shot echoplanar imaging sequence (echoplanar imaging factor 41, TR/TE 4000/89 ms, field of view 180×180 mm<sup>2</sup>, acquisition matrix 128×77, reconstruction matrix 256×256, 25 slices with thickness 4 mm without gap, and b-values of 0 and 1000 s/mm<sup>2</sup> in 3 orthogonal directions). Apparent diffusion coefficient (ADC) maps were created at the MR console.

The DTI protocol consisted of a single-shot echoplanar imaging sequence (echoplanar imaging factor 41, TR/TE 6817/87ms, field of view 190×190 mm<sup>2</sup>, acquisition matrix 96×96, reconstruction matrix 128×128, and 50 slices with thickness 2 mm without gap). Images were acquired in the axial plane with diffusion gradients applied in 32 noncollinear directions with a b-value of 800 s/mm<sup>2</sup> and 1 b=0 s/mm<sup>2</sup> image.

### Postprocessing

The ADC maps derived from the neonatal DWI data were analyzed with Osirix (www.osirix-viewer.com). Regions of interest (ROIs) were manually drawn in the anterior part of both cerebral peduncles, carefully avoiding any involvement of cerebrospinal fluid, as reported previously.<sup>4</sup> An asymmetry index (%) was calculated as follows: 100\*(ADC ischemic peduncle-ADC contralateral peduncle)/ADC contralateral peduncle.

DTI data were analyzed with ExploreDTI.<sup>10</sup> The DWIs were realigned to the b0-image to correct for eddy current induced geometric distortions and subject motion. In this procedure, the diffusion tensor was fitted for each voxel after adjusting the diffusion gradients with the proper b-matrix rotation.<sup>11</sup> To correct for any asymmetry in the axial plane due to the scan angulation, all DTI scans were rigidly transformed to Montreal Neurological Institute (MNI) space during this processing step.

Whole brain tractography was performed,<sup>12</sup> using a 1-mm step size. Propagation of the fibers was stopped if a voxel with a fractional anisotropy (FA) value <0.15 was entered or if the angle of a fiber between 2 consecutive steps exceeded 20°. ROIs were drawn on the directionally color-encoded FA map for each hemisphere separately in the cerebral peduncle, the posterior limb of the internal capsule (PLIC), and at the centrum semiovale. The ROI in the centrum semiovale was drawn 2 to 3 slices above the corpus callosum. In case tissue loss hindered specific drawing of any of the ROIs based on visible landmarks, a ROI was drawn based on the location and size of the corresponding ROI in the unaffected hemisphere. Fibers intersecting all 3 ROIs were retained for further analysis. Any fibers continuing into the other hemisphere, the cerebellum, and the medial lemniscus or single aberrant fibers were

removed. The FA, ADC, axial diffusivity ( $\lambda_1$ ), and radial diffusivity ( $\lambda_{23}$ ) were calculated for each CST separately as described previously<sup>13</sup> and used to calculate an asymmetry index.

### Assessment of Motor Development

The neurological outcome was evaluated at regular intervals after discharge as part of our follow-up program. Infants were seen at 3, 9, and 18 months and at later points in time when felt indicated. A pediatric physiotherapist (I.C.v.H.) who was unaware of the MRI results assessed postural and motor behavior. Gross motor development was assessed with items from Amiel-Tison<sup>14</sup> and Touwen.<sup>15</sup> Presence of UMD was assessed according to Claeys<sup>16</sup> and the manual ability classification system (MACS)<sup>17</sup> was used from 12 months onward. The MACS is a functional classification describing the voluntary hand use at a scale from 1 (handles objects easily and successfully) to 5 (does not handle objects).

To assess the additional value of acquiring DTI data at the age of 3 months in predicting motor outcome, we determined the likelihood of developing UMD based on the motor performance at 3 months. Infants were scored as having a normal, suspect, or abnormal performance, which was very likely to result in UMD. A suspect development included a directional preference of head rotation, hypotonia of the trunk, or asymmetrical lateral trunk tilting. Development was deemed abnormal if there was also one-sided fisting and/or a cortical thumb observed, asymmetry in voluntary movement of the extremities, or asymmetrical fidgety movements as described by Guzetta et al.<sup>18</sup>

### Statistical Analysis

Differences in clinical characteristics or MRI parameters were assessed using the Fisher exact test or the Mann-Whitney *U* test and were corrected for multiple comparisons with the Bonferroni correction using SPSS Version 18. The asymmetry indices of the neonatal ADC values were calculated twice to determine the intraclass correlation coefficient. Spearman correlation coefficient was used for ranked variables. Finally, receiver operator characteristic (ROC) curves were created using MedCalc Version 11.6 (MedCalc Software, Mariakerke, Belgium) to calculate cutoff values for determining the positive (PPV) and negative predictive values (NPV).

## Results

### Patients

Twenty-two infants who had DTI at 3 months of age were eligible for the study (Table 1). DWI was acquired in all infants but not suitable for interpretation in 2 infants. One infant's neonatal MRI showed an area of cavitation suggestive of an antenatally acquired main branch middle cerebral artery (MCA) stroke. A second infant suffered from a leaking giant aneurysm compressing the posterior cerebral artery, resulting in ischemia. The large amount of blood distorted the neonatal ADC map, which could therefore not be used.

### Motor Development

The median duration of follow-up for the infants who developed UMD was 18 months (range, 9–48 months). Infants with a normal neurodevelopmental outcome were last seen at a median age of 21 months (range, 16–48 months). At 3 months, 8 of 22 (36%) infants were classified as normal, 3 (14%) as suspect, and 11 (50%) as abnormal (Table 2). Of these 11 infants, 8 developed UMD (PPV 73%) with a MACS-I in 1, MACS-II in 5, and MACS-IV in 1 infant. One infant was too young to determine a reliable MACS. None of the children classified as normal or suspect developed UMD (NPV 100%).

**Table 1. Patient Characteristics, Displayed as Median and [Range]**

	Main MCA Branch	Other MCA Branches	PCA	P
Gender, M/F	4/2	4/7	3/2	NS
Gestational age, wk	39 <sup>+4</sup> [37 <sup>+1</sup> –41 <sup>+1</sup> ]	41 <sup>+0</sup> [37 <sup>+5</sup> –42 <sup>+2</sup> ]	39 <sup>+6</sup> [38 <sup>+0</sup> –41 <sup>+3</sup> ]	NS
Apgar score at 1 min	6 [2–9]	7 [1–10]	3 [0–6]	NS
Apgar score at 5 min	7 [3–10]	8 [4–10]	7 [5–9]	NS
Birth weight, g	3357 [2450–3500]	3390 [2305–4060]	3122 [2145–3880]	NS
UMD	6 (100%)	1 (9%)	1 (20%)	<0.01

MCA indicates middle cerebral artery; PCA, posterior cerebral artery; M/F, male/female; UMD, unilateral motor deficits; NS, nonsignificant.

**Neonatal DWI**

The neonatal scan was performed 2 to 7 days after birth in all subjects except for 1 infant who was scanned on day 21. This infant was resuscitated following cardiac surgery and MRI 5 days after the event showed a main branch MCA stroke.

Postnatal age at the time of scanning did not differ between the infants with a normal outcome and UMD.

MRI revealed a stroke in the territory of the main branch MCA in 6 infants. A MCA branch stroke was seen in 11 infants (4 posterior branch, 2 lenticulostriatal branches, and 5 cortical branch). The 5 remaining infants had a posterior cerebral artery stroke.

Asymmetry indices based on neonatal DWI could be calculated with an intraclass correlation coefficient of 0.95 (0.87–0.98). A larger ADC asymmetry at the level of the cerebral peduncle was found for the infants who developed UMD (Figure 1A, *P*=0.002).

Two infants stood out because their neonatal ADC map did show an asymmetry at the level of the cerebral peduncles, but no subsequent UMD was observed at later follow-up. One infant’s ADC map showed a lenticulostriate branch stroke with restricted diffusion in the striatum and descending CST (–28%; Figure 2A). A more thorough inspection of the second infant’s ADC map showed a region of low ADC values located more posteriorly and laterally in the cerebral peduncle, suggestive for affected ascending sensory tracts (–11%; Figure 2B). MRI at 3 months did indeed show a

cystic area in the primary sensory cortex with an intact primary motor cortex. (ROC) curve analysis resulted in a cutoff value of –11% and a PPV of 86%. None of the 13 infants with a normal cerebral peduncle developed UMD (NPV 100%).

**DTI at 3 Months of Age**

The median postnatal age at the second scan was 96 days (range, 82–127 days). The CSTs could be successfully visualized in 21 of 22 (95%) infants (Figure 3). Higher asymmetry indices were found for FA, ADC, and  $\lambda_{23}$  in the infants who developed UMD (*P*<0.001; Figure 1B). In 1 infant with a main branch MCA stroke who developed UMD, the affected CST could not be visualized. This infant’s neonatal DWI showed an asymmetry of 39% and conventional imaging at 3 months showed a large area of cavitation without a PLIC on the affected side. ROC curve analysis computed a cutoff value of 6%. Using this cutoff, DTI-based tractography was able to predict the long-term outcome correctly in all infants (PPV 100%, NPV 100%). This included the infants who did not develop UMD but presented with an abnormal motor repertoire at 3 months or showed an asymmetry on the neonatal DWI. In the UMD group, a significant correlation was found between the MACS and FA asymmetry (*r*=–.80, *P*<0.05).

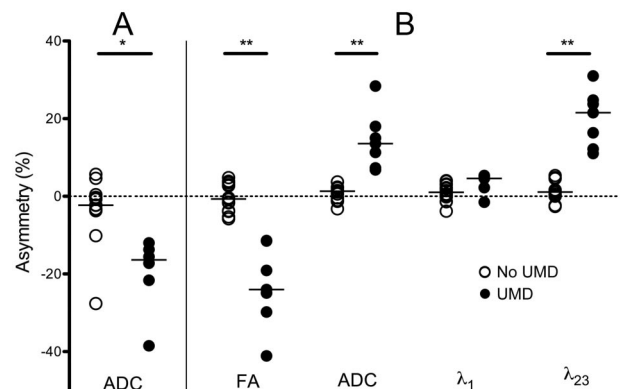
Because development of UMD is most likely to occur after a PAIS in the MCA territory with CST involvement, predic-

**Table 2. Asymmetry in Neonatal DWI and DTI Parameters at 3 Months Versus Motor Score at 3 Months of Age for Infants With a MCA Territory (○/●) or PCA Territory Stroke (Δ/▲)\***

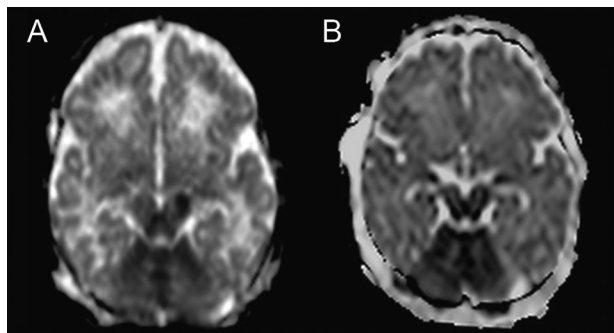
Clinical Assessment at 3 Mo	DWI (ADC Asymmetry)			DTI (FA Asymmetry)	
	≤11%	>11%	Not Suitable	≤6%	>6%
Normal	○○○○			○○○○	
	○○ΔΔ			○○ΔΔ	
Suspect	○○Δ			○○Δ	
Abnormal	○Δ	●●●●	●▲	○○Δ	●●●●
		●●●●			●●●●▲

DWI indicates diffusion-weighted imaging; DTI, diffusion tensor imaging; MCA, middle cerebral artery; PCA, posterior cerebral artery; ADC, apparent diffusion coefficient; FA, fractional anisotropy; UMD, unilateral motor deficits; CST, corticospinal tract.

\*Open symbols represent the infants who did not develop UMD, whereas the filled symbols represent the infants who did develop UMD. The infant in whom no affected CST could be visualized with DTI-based tractography was regarded as having an asymmetry of >6%.



**Figure 1.** Asymmetry indices of neonatal ADC values at the level of the cerebral peduncle (A) and DTI parameters of the CST (B) for infants with a normal outcome and for infants who developed UMD (\**P*<0.002, \*\**P*<0.001). The DTI data of the infant whose affected CST could not be visualized were not included. ADC indicates apparent diffusion coefficient; DTI, diffusion tensor imaging; CST, corticospinal tract; UMD, unilateral motor deficits; FA, fractional anisotropy.



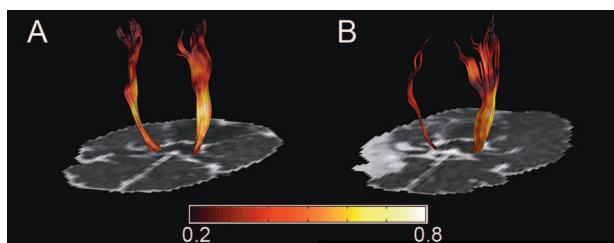
**Figure 2.** DWI of the 2 infants with an asymmetrical neonatal ADC value without subsequent development of UMD. DWI indicates diffusion-weighted imaging; ADC, apparent diffusion coefficient; UMD, unilateral motor deficit.

tive values were also calculated for the MCA subgroup separately. The PPV and NPV did not differ for DWI and DTI in this subgroup. For the motor assessment at 3 months, only the PPV increased to 78%.

### Discussion

This study shows that both DWI in the neonatal period and evaluation of motor behavior at 3 months of age have a high PPV, which is in line with previous findings.<sup>3–5,18,19</sup> However, only DTI at 3 months of age reached a PPV of 100% and was able to predict a correct outcome for all infants. DTI was of additional value in the infants whose neonatal DWI was inconclusive and in the infants with an unexpected suspect or abnormal motor repertoire at 3 months of age. This implies that in the absence of a neonatal DWI or when the early motor repertoire is suspect, DTI may assist in predicting outcome.

Predicting motor outcome after PAIS has been the focus of several neuroimaging studies. The predictive value of the size and the location of the lesion on conventional MRI was found to be good in the presence of hemispheric, internal capsule, and basal ganglia involvement<sup>2,20,21</sup> and was further improved after the introduction of DWI.<sup>3,4</sup> Studies reporting the role of DTI after perinatal brain injury mostly included children who already showed evidence of motor problems at the time of the MRI. Glenn et al<sup>8</sup> studied 15 children with UMD due to varying etiologies and compared DTI parameters of the CSTs with those of a control group. The clinical severity of UMD correlated with asymmetry in FA, ADC, and  $\lambda_{23}$ . The same group studied infants with motor dysfunction and reported lower FA and higher ADC values in infants who developed a



**Figure 3.** CSTs of an infant with a normal outcome (A) and an infant who developed UMD (B). The DTI of the infant with UMD shows a clear asymmetry in FA, represented by the color intensity. CSTs indicates corticospinal tracts; UMD, unilateral motor deficits; DTI, diffusion tensor imaging; FA, fractional anisotropy.

poor motor outcome.<sup>9</sup> Murakami et al<sup>22</sup> reported differences in FA in a group of 10 infants with UMD due to periventricular leukomalacia when scanned during late infancy/early childhood.

Few studies reported the use of DTI in predicting motor outcome<sup>9,23</sup> and to the best of our knowledge, only Van Pul et al<sup>23</sup> correlated DTI findings after PAIS with long-term motor outcome. In their study, 2 of 10 (20%) infants with hypoxic–ischemic encephalopathy showed a MCA stroke. DTI-based tractography at 3 months of age revealed a low FA of the affected CST, and both infants developed UMD.

A number of studies have reported decreased FA and ADC values when performing ROI analysis on neonatal DTI data of infants with perinatal hypoxic ischemia.<sup>24–26</sup> Two studies correlated these findings with neurodevelopmental outcome during the first weeks of life<sup>25</sup> up to months,<sup>24</sup> but none reported long-term outcome, including the development of UMD.

Chronic changes in DTI parameters have also been reported in animal models and correlated to the underlying histopathology.<sup>27–29</sup> The decreased FA and increased  $\lambda_{23}$  as found in our study may be reflective of decreased myelination.<sup>28</sup> Changes in  $\lambda_1$  have been found in some<sup>27</sup> but not all animal models.<sup>29</sup> We did not find any significant difference in  $\lambda_1$ , which is in line with previous DTI studies in children.<sup>8,9</sup>

Asymmetry of DTI parameters has been correlated with an increase in severity of motor impairments.<sup>8,9</sup> Our data suggest that an increase in FA asymmetry corresponds with a decrease in the manual ability as measured with the MACS. However, these findings should be interpreted with caution because the number of infants studied was relatively small and classifying the severity of UMD at this early age is difficult.<sup>30</sup> In addition, interpretation may be further complicated by other confounds related to the diffusion tensor model such as crossing fibers or the partial volume effect.<sup>31,32</sup>

DTI parameters change rapidly during childhood.<sup>33</sup> The relatively wide spread in postnatal age at the time of the second scan (84–127 days) might therefore introduce a confounding factor when comparing the raw DTI parameters between infants with and without UMD. By using an asymmetry index, we tried to overcome this confounder. This index, however, assumes that the contralateral hemisphere is not affected. Therefore, infants with bilateral ischemia were not included. In the absence of an unaffected contralateral hemisphere, age-matched reference values of healthy infants would be required to predict outcome with DTI.

Extensive (video) evaluation of general movements and hand movements at 3 months of age is helpful to predict the development of UMD.<sup>18,19</sup> It might be that such a detailed assessment of motor behavior would limit the role of DTI at this age in predicting the development of UMD. The motor function data of our study were collected as part of the standard clinical care at our follow-up clinic and did therefore not include such an extensive evaluation.

### Conclusions

DTI-based tractography at 3 months can be used to predict neurodevelopmental outcome after PAIS. It has a similar predictive value as DWI in the neonatal period and can

especially be of additional value in case of an indecisive neonatal DWI or unexpected abnormal early motor development.

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### References

- Kirton A, deVeber G. Advances in perinatal ischemic stroke. *Pediatr Neurol*. 2009;40:205–214.
- Mercuri E, Barnett A, Rutherford M, Guzzetta A, Haataja L, Cioni G, et al. Neonatal cerebral infarction and neuromotor outcome at school age. *Pediatrics*. 2004;113:95–100.
- Kirton A, Shroff M, Visvanathan T, deVeber G. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke*. 2007;38:974–980.
- de Vries LS, van der Grond J, van Haastert IC, Groenendaal F. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics*. 2005;36:12–20.
- Husson B, Hertz-Pannier L, Renaud C, Allard D, Presles E, Landrieu P, et al. Motor outcomes after neonatal arterial ischemic stroke related to early MRI data in a prospective study. *Pediatrics*. 2010;126:912–918.
- Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J*. 1994;66:259–267.
- Tournier JD, Mori S, Leemans A. Diffusion tensor imaging and beyond. *Magn Reson Med*. 2011;65:1532–1556.
- Glenn OA, Ludeman NA, Berman JI, Wu YW, Lu Y, Bartha AI, et al. Diffusion tensor MR imaging tractography of the pyramidal tracts correlates with clinical motor function in children with congenital hemiparesis. *AJNR Am J Neuroradiol*. 2007;28:1796–1802.
- Ludeman NA, Berman JI, Wu YW, Jeremy RJ, Kornak J, Bartha AI, et al. Diffusion tensor imaging of the pyramidal tracts in infants with motor dysfunction. *Neurology*. 2008;71:1676–1682.
- Leemans A, Jeurissen B, Sijbers J, Jones DK. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. 17th Annual Meeting of Intl Soc Mag Reson Med, Hawaii, April 18–24. 2009:3537.
- Leemans A, Jones DK. The b-matrix must be rotated when correcting for subject motion in DTI data. *Magn Reson Med*. 2009;61:1336–1349.
- Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med*. 2000;44:625–632.
- Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Microstructural maturation of the human brain from childhood to adulthood. *Neuroimage*. 2008;40:1044–1055.
- Amiel-Tison C, Grenier A. *Neurological Assessment During the First Year of Life*. Oxford: Masson; 1986.
- Touwen BLC. *Examination of the Child With Minor Neurological Dysfunction*. London: SIMP/Heinemann; 1979.
- Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, et al. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol*. 2005;47:571–576.
- Plasschaert VF, Ketelaar M, Nijhuis MG, Enkelaar L, Gorter JW. Classification of manual abilities in children with cerebral palsy under 5 years of age: how reliable is the manual ability classification system? *Clin Rehabil*. 2009;23:164–170.
- Guzzetta A, Mercuri E, Rapisardi G, Ferrari F, Roversi MF, Cowan F, et al. General movements detect early signs of hemiplegia in term infants with neonatal cerebral infarction. *Neuropediatrics*. 2003;34:61–66.
- Guzzetta A, Pizzardi A, Belmonti V, Boldrini A, Carotenuto M, D'Acunto G, et al. Hand movements at 3 months predict later hemiplegia in term infants with neonatal cerebral infarction. *Dev Med Child Neurol*. 2010;52:767–772.
- Mercuri E, Rutherford M, Cowan F, Pennock J, Counsell S, Papadimitriou M, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. *Pediatrics*. 1999;103:39–46.
- Lee J, Croen LA, Lindan C, Nash KB, Yoshida CK, Ferriero DM, et al. Predictors of outcome in perinatal arterial stroke: a population-based study. *Ann Neurol*. 2005;58:303–308.
- Murakami A, Morimoto M, Yamada K, Kizu O, Nishimura A, Nishimura T, et al. Fiber-tracking techniques can predict the degree of neurologic impairment for periventricular leukomalacia. *Pediatrics*. 2008;122:500–506.
- van Pul C, Buijs J, Vilanova A, Roos FG, Wijn PF. Infants with perinatal hypoxic ischemia: feasibility of fiber tracking at birth and 3 months. *Radiology*. 2006;240:203–214.
- Malik GK, Trivedi R, Gupta RK, Hasan KM, Hasan M, Gupta A, et al. Serial quantitative diffusion tensor MRI of the term neonates with hypoxic-ischemic encephalopathy (HIE). *Neuropediatrics*. 2006;37:337–343.
- Brissaud O, Amirault M, Villega F, Periot O, Chateil JF, Allard M. Efficiency of fractional anisotropy and apparent diffusion coefficient on diffusion tensor imaging in prognosis of neonates with hypoxic-ischemic encephalopathy: a methodologic prospective pilot study. *AJNR Am J Neuroradiol*. 2010;31:282–287.
- Ward P, Counsell S, Allsop J, Cowan F, Shen Y, Edwards D, et al. Reduced fractional anisotropy on diffusion tensor magnetic resonance imaging after hypoxic-ischemic encephalopathy. *Pediatrics*. 2006;117:e619–e630.
- Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage*. 2003;20:1714–1722.
- Wang S, Wu EX, Cai K, Lau HF, Cheung PT, Khong PL. Mild hypoxic-ischemic injury in the neonatal rat brain: longitudinal evaluation of white matter using diffusion tensor MR imaging. *AJNR Am J Neuroradiol*. 2009;30:1907–1913.
- Shereen A, Nemkul N, Yang D, Adhami F, Dunn RS, Hazen ML, et al. Ex vivo diffusion tensor imaging and neuropathological correlation in a murine model of hypoxia-ischemia-induced thrombotic stroke. *J Cereb Blood Flow Metab*. 2011;31:1155–1169.
- Nelson KB, Ellenberg JH. Children who 'outgrew' cerebral palsy. *Pediatrics*. 1982;69:529–536.
- Wheeler-Kingshott CA, Cercignani M. About 'axial' and 'radial' diffusivities. *Magn Reson Med*. 2009;61:1255–1260.
- Vos SB, Jones DK, Viergever MA, Leemans A. Partial volume effect as a hidden covariate in DTI analyses. *Neuroimage*. 2011;55:1566–1576.
- Hermoye L, Saint-Martin C, Cosnard G, Lee SK, Kim J, Nassogne MC, et al. Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *Neuroimage*. 2006;29:493–504.

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