doi:10.1093/brain/awn268 *Brain* (2008), **131**, 3201–3208

Specific relations between neurodevelopmental abilities and white matter microstructure in children born preterm

Serena J. Counsell,[1,2] A. David Edwards,[1,2,3] Andrew T. M. Chew,[2,3] Mustafa Anjari,[1,2] Leigh E. Dyet,[1,2,3] Latha Srinivasan,[1,2,3] James P. Boardman,[1,2,3] Joanna M. Allsop,[1,2] Joseph V. Hajnal,[1,2] Mary A. Rutherford[1,2,3] and Frances M. Cowan[2,3]

[1]Imaging Sciences Department, MRC Clinical Sciences Centre,[2]Hammersmith/St Mary's Comprehensive Biomedical Research Centre, DuCane Road, London, W12 0HS and [3]Department of Paediatrics, Imperial College London, Hammersmith Campus, UK

Correspondence to: Dr Serena J. Counsell, Robert Steiner MR Unit, Imaging Sciences Department, Imperial College London, Hammersmith Hospital, DuCane Road, London W12 0HS, UK
E-mail: serena.counsell@imperial.ac.uk

Survivors of preterm birth have a high incidence of neurodevelopmental impairment which is not explained by currently understood brain abnormalities. The aim of this study was to test the hypothesis that the neurodevelopmental abilities of 2-year-old children who were born preterm and who had no evidence of focal abnormality on conventional MR imaging were consistently linearly related to specific local changes in white matter microstructure. We studied 33 children, born at a median (range) gestational age of 28^{+5} (24^{+4}–32^{+1}) weeks. The children were recruited as infants from the Neonatal Intensive Care Unit at Queen Charlotte's and Hammersmith Hospital in the early neonatal period and imaged at a median corrected age of 25.5 (24–27) months. The children underwent diffusion tensor imaging to measure fractional anisotropy (FA) as a measure of tissue microstructure, and neurodevelopmental assessment using the Griffiths Mental Development Scales [giving an overall developmental quotient (DQ) and sub-quotients scores for motor, personal–social, hearing–language, eye–hand coordination and performance scales] at 2 years corrected age. Tract-based spatial statistics with linear regression analysis of voxel-wise cross-subject statistics were used to assess the relationship between FA and DQ/sub-quotient scores and results confirmed by reduced major axis regression of regions with significant correlations. We found that DQ was linearly related to FA values in parts of the corpus callosum; performance sub-scores to FA values in the corpus callosum and right cingulum; and eye–hand coordination sub-scores to FA values in the cingulum, fornix, anterior commissure, corpus callosum and right uncinate fasciculus. This study shows that specific neurodevelopmental impairments in infants born preterm are precisely related to microstructural abnormalities in particular regions of cerebral white matter which are consistent between individuals. FA may aid prognostication and provide a biomarker for therapeutic or mechanistic studies of preterm brain injury.

Keywords: preterm; infant; brain; diffusion tensor imaging; white matter

Abbreviations: DTI = diffusion tensor imaging; DQ = developmental quotient; FA = fractional anisotropy; MR = magnetic resonance; TBSS = Tract-based spatial statistics

Received May 1, 2008. Revised August 15, 2008. Accepted September 22, 2008. Advance Access publication October 24, 2008

Introduction

The incidence of preterm birth is increasing and mortality rates have decreased in recent years (Langhoff-Roos *et al.*, 2006). However, the increasing number of children who survive preterm birth continue to have a high prevalence of neurodevelopmental impairment, including cognitive deficits, developmental coordination disorder, behavioural problems such as attention deficit hyperactivity disorder and lower academic performance at school age (Bhutta *et al.*, 2002; Marlow *et al.*, 2005). These functional deficits

are not explained by focal brain lesions detected by cranial ultrasonography or conventional magnetic resonance (MR) imaging, and although quantitative MR imaging has identified regions of grey and white matter volume loss which appear to be correlated with specific learning or behavioural problems (Isaacs *et al.*, 2000; Peterson *et al.*, 2000; Inder *et al.*, 2005; Woodward *et al.*, 2005; Kapellou *et al.*, 2006), the pathogenesis of this impaired growth is unclear.

However, the commonest abnormality detected by MR imaging in preterm infants is diffuse excessive high signal on T_2-weighed imaging of white matter, which occurs to some degree in about three quarters of preterm infants (Maalouf *et al.*, 1999) and is loosely associated with tissue volume loss (Boardman *et al.*, 2006) and neurodevelopmental impairment (Dyet *et al.*, 2006). It is widely hypothesized that this reflects white matter microstructural damage which is a primary cause of neurodevelopmental impairment (Volpe, 2003).

Cerebral white matter microstructure can be investigated by diffusion tensor imaging (DTI), which assesses the Brownian motion of water in tissue (Le Bihan *et al.*, 1986). DTI can detect microstructural abnormalities which are not always apparent on conventional MR imaging: fractional anisotropy (FA), derived from DTI, assesses the directional dependence of diffusion in tissue, where water moves more freely parallel to white matter fibres than perpendicular to them. This gives a useful measure of tissue microstructure that is dependent on a number of factors including fibre coherence, axonal density, cell membranes and myelination (Moseley *et al.*, 1990; Beaulieu, 2002).

DTI studies have demonstrated a correlation between reduced FA in white matter regions and lower cognitive abilities in older children and adolescents. Increases in FA between 8 and 18 years of age in healthy children are associated with increases in working memory and reading ability (Nagy *et al.*, 2004). Low FA values in specific white matter regions are related to motor, cognitive, perceptual and mental health impairments in adolescents who were born preterm (Skranes *et al.*, 2007). In addition, Yung recently observed that the mean FA of the whole brain white matter in children (aged between 8.8 and 11.5 years) who were born preterm correlated with full scale IQ scores (Yung *et al.*, 2007). To date, there have been no studies assessing white matter microstructure and neurodevelopmental ability in preterm children who have no evidence of focal abnormality on MR imaging as young as 2 years of age.

Tract-based spatial statistics (TBSS) now provides a novel technique to determine whether neurodevelopmental impairment in children born preterm is linearly related to specific stereotypical white matter microstructural abnormalities. TBSS is an automated, observer-independent approach for assessing FA in the major white matter tracts on a voxel-wise basis across groups of subjects (Smith *et al.*, 2006) which we have previously applied to investigate microstructure in preterm infants at term equivalent age (Anjari *et al.*, 2007). The aim of the present study was to test the hypothesis that the neurodevelopmental abilities of 2-year-old children who were born preterm and who had no evidence of focal abnormality on conventional MR imaging were precisely and linearly related to specific and characteristic local changes in white matter microstructure.

Methods

This study was approved by the local Research Ethics Committee and written parental consent was obtained prior to scanning.

Subjects

We studied 33 children (18 male) who were born at a median (range) gestational age of 28^{+5} (24^{+4}–32^{+1}) weeks and median birth weight of 1.08 kg (0.745–1.94), between 2003 and 2005. The children were recruited as infants from the Neonatal Intensive Care Unit at Queen Charlotte's and Hammersmith Hospital in the early neonatal period and imaged at a median corrected age of 25.5 (24–27) months. Table 1 shows the perinatal characteristics of the infants. Inclusion criteria for this study were GA at birth $\leqslant 32$ weeks, neurodevelopmental assessment at 2 years corrected age and DTI examination at 3 T at 2 years corrected age. Infants with overt focal lesions or post- haemorrhagic hydrocephalus on neonatal MRI examination, congenital abnormalities or metabolic disease were excluded.

A total of 371 infants were born at $\leqslant 32$ weeks GA at Queen Charlotte's and Hammersmith Hospital between 2003 and 2005, and 339 of these infants survived to term equivalent age. Approximately one-third of these infants returned to their referring hospital prior to term equivalent age. Of the remainder, 90 infants were recruited into an ongoing MRI research study assessing brain development. Of these infants, 22 were excluded because of abnormalities on their neonatal MRI examinations (five cystic periventricular leucomalacia, 13 haemorrhagic periventricular infarction, three post-haemorrhagic ventriculomegaly and one basal ganglia lesions). One infant was excluded because of a chromosomal abnormality, two because of congenital brain malformations and one because of neonatally identified cytomegalovirus. Eight infants (including three sets of twins) attended for

Table 1 Perinatal characteristics of the infants

GA, median (range)	28^{+5} (24^{+4}–32^{+1})
Birthweight, median (range)	1.08 (0.745–1.94) kg
Head circumference at birth, median (range)	27 (22.5–32.3) cm
Number of intra-uterine growth restricted infants (<10th centile)	9
Number of infants who had postnatal sepsis	10
Number of days to full enteral feeds, median (range)	7 (2–25)
Number of infants with chronic lung disease[a]	8
Number of infants who had necrotizing enterocolitis	2
Number of infants with patent ductus arteriosus	2

[a]Defined as requiring supplemental oxygen at 28 days after birth.

their 2-year neurodevelopmental assessment but their parents did not wish them to have an MRI examination; one set of twins attended for neurodevelopmental assessment but were unwell and so did not have an MRI; seven infants had moved too far away to be able to attend for a scan; one infant was lost to follow-up; three infants (including one set of twins) did not attend for either neurodevelopmental assessment or DTI; four infants had MRI but DTI was not acquired and DTI images of six infants were degraded due to motion artefact. This left 33 infants eligible for the study.

Imaging

MR imaging was performed on a Philips 3-T system with maximum gradient strength of 62 mT/m on each independent axis and slew rate of 100 mT/m/ms on each axis using a six-channel phased array head coil. The children were sedated for imaging using oral chloral hydrate (100 mg/kg up to a maximum of 1 g) after an assessment by an experienced paediatrician (including a measure of oxygen saturation, heart rate, temperature and respiratory rate) and had been fasting for 4 h. Ear protection was used and the head was immobilized using a pillow filled with polystyrene beads, from which the air was evacuated. Their oxygen saturation and electrocardiograph were monitored throughout the scan, and a paediatrician trained in MRI procedures was always in attendance. After imaging oxygen saturation was monitored until children were awake and able to feed; all children went home the same day.

3D MPRAGE and 3D dual echo-weighted imaging were obtained prior to DTI. Single shot echo planar DTI was acquired in 15 non-collinear directions using the following parameters; TR 9000 ms, TE 49 ms, slice thickness 2 mm, field of view 224 mm, matrix 128×128 (voxel size $= 1.75 \times 1.75 \times 2\,mm^3$), b value $= 750\,s/mm^2$. The data were acquired with a SENSE factor of two and the scanning time for this sequence was 5 min.

Neurodevelopmental assessment

All infants had a neurodevelopmental assessment using the Griffiths Mental Development Scales (Revised) (Huntley, 1996) performed on the same day as their MRI examination at 2 years corrected age. The mean (± SD) developmental quotient (DQ) score for the general population is 100 (±12). For those achieving over 2 years the revised 2–8 years Griffiths scales were used, scores from the younger scales increased appropriately and overall DQ then calculated. The assessments were performed by experienced, appropriately trained paediatricians blinded to the brain MRI findings. The Griffiths Mental Development Scales provide an overall DQ with subscales assessing skill areas [locomotor, personal–social, hearing–language, eye–hand coordination and performance (and practical reasoning for those achieving over 2 years)]. The children had also been examined between 9 and 18 months using a standardized scoreable neurological examination which at this age can be used to predict functional motor outcome (Haataja *et al.*, 1999; Frisone *et al.*, 2002; Bax *et al.*, 2005). The children were re-examined at their 2 year visit and evidence of cerebral palsy was specifically looked for (Bax *et al.*, 2005).

Data analysis

Data analysis was performed using FMRIB's software library (FSL) (Smith *et al.*, 2004). Image artefacts due to eddy current distortions were minimized by registering the DT images to the b0 images. The DTI data were skull stripped and FA maps were produced using FMRIB's diffusion toolbox (FDT). Voxel-wise statistical analysis of the FA data was carried out using TBSS implemented in FSL (Smith *et al.*, 2006). First, FA data were aligned into a common space using a non-linear registration algorithm (www.doc.ic.ac.uk/~dr/software). Then the mean FA image was created and thinned to generate a mean FA skeleton which represented the centres of all tracts common to the group. This was thresholded to FA $\geqslant 0.20$ to include the major white matter pathways but exclude peripheral tracts where there was significant inter-subject variability and/or partial volume effects with grey matter. Each subject's aligned FA data were then projected onto this skeleton.

The relationship between FA and DQ scores was assessed using linear regression analysis of voxel-wise cross-subject statistics corrected for multiple comparisons using cluster-based thresholding ($c \geqslant 3$, $P < 0.01$). In addition, FA values were assessed for each sub-scale of the Griffiths Mental Development Scales (locomotor, personal–social, hearing–language, eye–hand coordination and performance). As few children had scores from the practical reasoning scale (only for those achieving over 2 years), this was used to assess the overall DQ but we did not correlate this scale individually with FA values.

In order to confirm and to visualize the relation between local tissue abnormalities and specific neurodevelopmental abilities, regions of interest were generated from clusters that demonstrated a significant correlation with FA ($c \geqslant 3$, $P < 0.01$) and subjected to univariate regression analysis. Both FA and neurodevelopmental variables were measured with errors and although this does not affect hypothesis testing for correlations, it may cause standard linear regression (which assumes that the abscissa variable is measured without error) to produce a biased estimate of slope unless variance on the abscissa is much less than on the ordinate. The variance in FA could be determined, and is shown in the figures, but no estimation of the error in the neurodevelopmental scoring was possible. We therefore calculated gradients using reduced major axis regression analysis which allows for variance in both ordinate and abscissa [Stata 9.2: command *sdline* with bootstrap estimation of confidence limits (100 iterations)]. The Bonferroni correction for multiple significance testing was applied to reported P-values.

Results

Conventional MRI findings

Term equivalent age; nine infants had normal imaging findings, 24 had evidence of DEHSI, 14 had ventricular dilatation (13 mild, one moderate), five had an increased extracerebral space, six had evidence of previous germinal layer haemorrhage and one had evidence of previous intraventricular haemorrhage.

Two years corrected age: five infants had normal imaging appearances, 20 had minimal increased T_2 in the posterior periventricular white matter, 16 had ventricular dilatation (13 mild, three moderate), one had an increased extracerebral space and 19 had thinning of the body of the corpus callosum. These are common imaging findings in infants who were born preterm.

Neurodevelopmental assessment scores

The mean ± SD DQ score at 2 years corrected age was 107 ± 15 and the mean values for the subscales were: locomotor 113 ± 17; personal and social 109 ± 17; hearing and language 101 ± 26; eye–hand coordination 98 ± 15; and performance 109 ± 23. The median (range) optimality score obtained at neurological examination between 9 and 18 months was 75 (68–78). No child had evidence of cerebral palsy or other major motor deficit at 2 years. DQ and subscale scores were not significantly different between male and female infants (DQ, $P = 0.90$; locomotor, $P = 0.98$; personal–social, $P = 0.11$; hearing–language, $P = 0.10$; eye–hand coordination, $P = 0.25$; and performance, $P = 0.90$).

Correlation between neurodevelopmental assessment scores and local white matter microstructure

TBSS showed that FA values in the isthmus and the body of the corpus callosum were significantly correlated to overall DQ scores (119 voxels) (Fig. 1). We found that performance sub-scores were related to FA values in the corpus callosum (188 voxels) and right cingulum (32 voxels) (Fig. 2). Eye–hand coordination sub-scores were correlated to FA values in the cingulum bilaterally (left, 46 voxels; right, 56 voxels), the fornix (25 voxels), the anterior commissure (45 voxels), the corpus callosum (326 voxels) and the right uncinate fasciculus (25 voxels) (Fig. 3). There was no correlation between FA values and locomotor, personal–social or hearing–language scores.

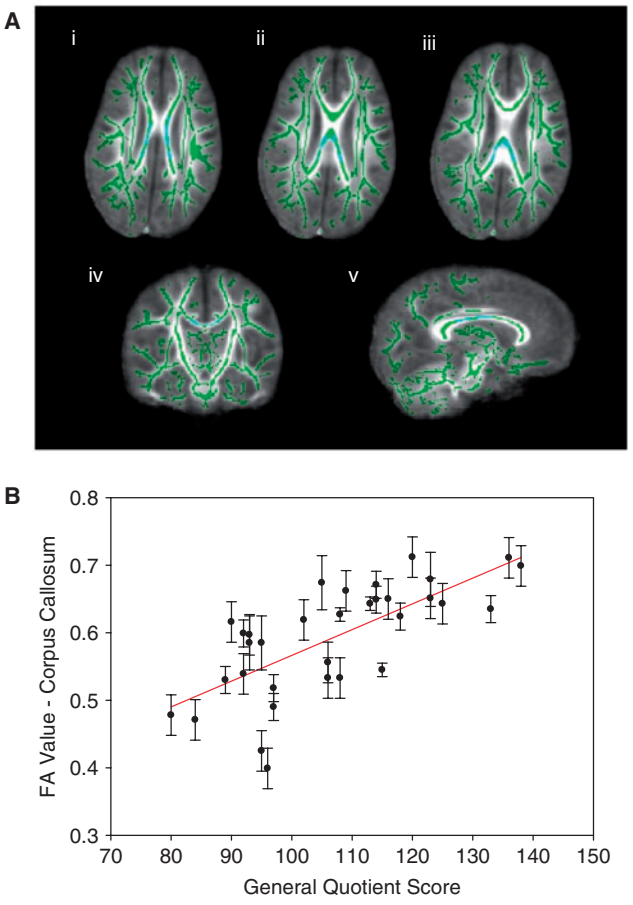

Fig. 1 (**A**) Mean FA skeleton (green) overlaid on mean FA map in axial (i–iii), coronal (iv) and sagittal (v) plane. Voxels showing a significant correlation ($c \geqslant 3$, $P < 0.01$) between FA and DQ are shown in blue and include the body and isthmus of the corpus callosum. (**B**) Graph demonstrating correlation between FA and DQ in voxels shown in blue in (**A**).

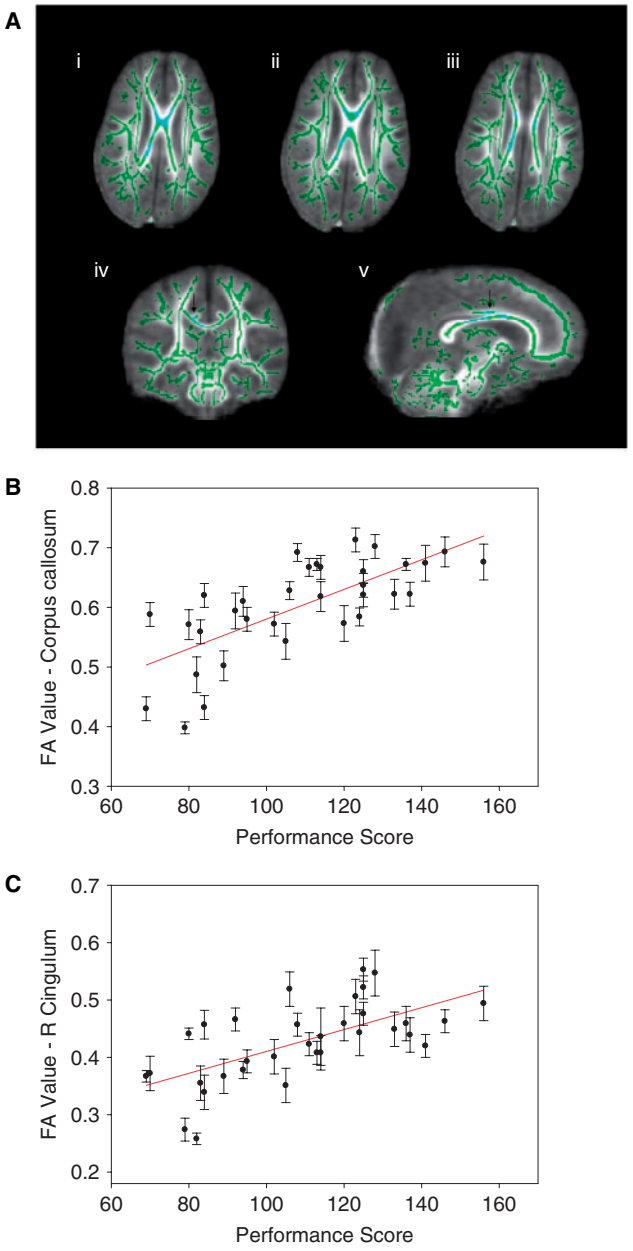

Fig. 2 (**A**) Mean FA skeleton (green) overlaid on mean FA map in axial (i–iii), coronal (iv) and sagittal (v) plane. Voxels showing a significant correlation ($c \geqslant 3$, $P < 0.01$) between FA and performance are shown in blue and include the corpus callosum and right cingulum (black arrow). (**B**) and (**C**) Graphs demonstrating correlation between FA and performance in voxels shown in blue in (**A**) in the (**B**) corpus callosum, (**C**) right cingulum.

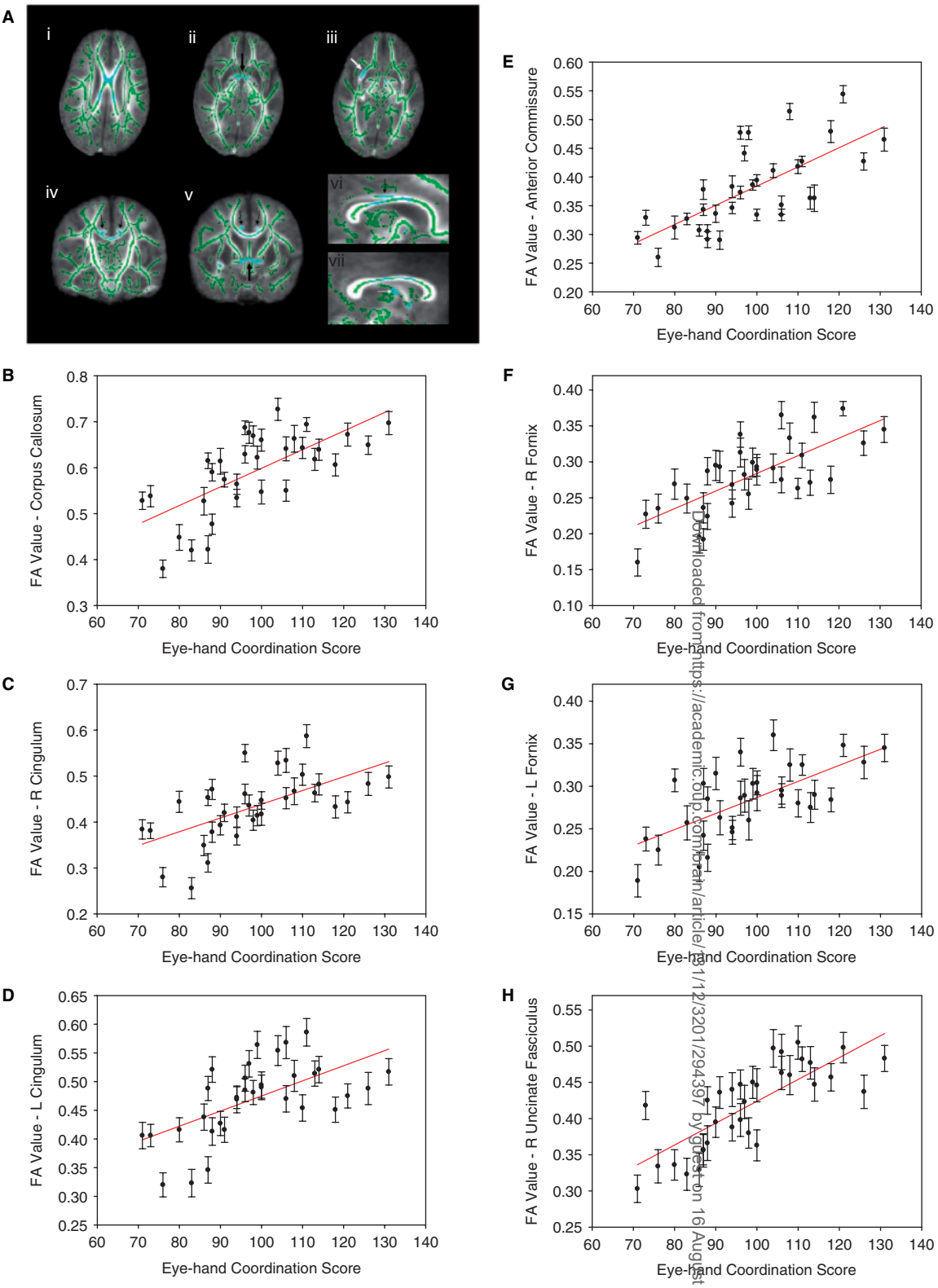

Fig. 3 (**A**) Mean FA skeleton (green) overlaid on mean FA map in axial (i–iii), coronal (iv and v) and sagittal (vi and vii) plane. Voxels showing a significant correlation ($c \geqslant 3$, $P < 0.01$) between FA and eye–hand coordination are shown in blue and include the corpus callosum (i), cingulum (thin black arrows, iv, v, vi), anterior commissure (thick black arrow, ii and v), fornix (thin white arrow, vii) and the right uncinate fasciculus (thick white arrow, iii). (**B–H**) Graphs demonstrating correlation between FA and eye–hand coordination score in voxels shown in blue (**A**) in the (**B**). corpus callosum, (**C**) right cingulum, (**D**) left cingulum, (**E**) anterior commissure, (**F**) right fornix, (**G**) left fornix, (**H**) right uncinate fasciculus.

Table 2 Results of reduced major axis regression analyses of FA versus DQ/sub-scale score for the regions demonstrating a significant correlation with FA ($c \geqslant 3$, $P < 0.01$)

Neurodevelopmental assessment test	Region	*P*	Slope	95% confidence interval
Developmental quotient	Corpus callosum	<0.001	0.00541	0.00210–0.00358
Performance	Corpus callosum	<0.001	0.00348	0.00249–0.00446
Performance	Right cingulum	<0.001	0.00300	0.00207–0.00394
Eye-hand coordination	Right cingulum	<0.001	0.00491	0.00316–0.00666
Eye-hand coordination	Left cingulum	<0.001	0.00443	0.00294–0.00592
Eye-hand coordination	Right fornix	<0.001	0.00341	0.00250–0.00433
Eye-hand coordination	Left fornix	<0.001	0.00284	0.00210–0.00358
Eye-hand coordination	Anterior commisure	<0.001	0.00479	0.00356–0.00602
Eye-hand coordination	Corpus callosum	<0.001	0.00597	0.00418–0.00776
Eye-hand coordination	Right uncinate fasciculus	<0.001	0.00393	0.00289–0.00497

Univariate analysis of each region of interest derived from the TBSS survey confirmed significant relations between FA and neurodevelopmental ability, which were consistent between regions. The slopes of these relations are given in Table 2.

Discussion

TBSS provides an objective and reproducible voxel-wise survey of cerebral white matter which reveals local features consistent across a group of subjects and avoids problems involved in subjective selection of locations of interest or hypothesis-based selection of brain regions (Smith *et al.*, 2006). In this study it demonstrated that in children born preterm white matter microstructure, as determined by FA, have a particular regional pattern that is consistent between individuals and related to specific neurodevelopmental impairments.

Reductions in FA may reflect: reductions in myelination; axonal damage; or decreased fibre coherence. A number of studies have documented that on average FA values are lower in the brains of preterm infants around term-corrected age than their term-born peers (Huppi *et al.*, 1998; Neil *et al.*, 1998; Miller *et al.*, 2002; Counsell *et al.*, 2006). This implies that the abnormalities detected in the present study reflect earlier events, and further studies show that the changes persist into later childhood (Nagy *et al.*, 2003) and adolescence (Vangberg *et al.*, 2006), emphasizing the importance of early microstructural development.

At the resolution achievable *in vivo*, the imaging voxels will inevitably contain fibre populations with different orientations, resulting in a reduction in the measured FA value.

By thresholding our data to include only tracts with FA values $\geqslant 0.20$, we confined our analysis to major white matter tracts, where fibre coherence is relatively high and crossing fibres are less prevalent. This has the additional advantage of excluding tracts where intra-subject variation is greatest (Smith *et al.*, 2006). However, this prevented us from assessing regions of low anisotropy such as central grey matter. A further limitation of this approach is that TBSS is not always able assess white matter where there is an abrupt change in direction of the fibre pathway, for example at the junction of tracts (Smith *et al.*, 2006).

The detection of microstructural abnormalities related to overall DQ in the corpus callosum is consistent with previous structural MR studies which demonstrated an association between preterm birth and reduced corpus callosum volume (Cooke and Abernethy, 1999; Stewart *et al.*, 1999; Peterson *et al.*, 2000; Rademaker *et al.*, 2004). Callosal size appears to be associated with specific performance measures including verbal IQ and fluency scores in male adolescents (Nosarti *et al.*, 2004), motor function (Rademaker *et al.*, 2004), performance and verbal IQ (Peterson *et al.*, 2000) and visual–motor integration skills in older children (Peterson *et al.*, 2000; Rademaker *et al.*, 2004). The present study provides an explanation for these findings being due to local white matter microstructural abnormality in the corpus callosum. Again, these changes are probably initiated earlier as we have previously found specific reductions in FA in the corpus callosum of preterm infants imaged at term compared to term-born control infants using TBSS (Anjari *et al.*, 2007) and sub-optimal growth of the corpus callosum has been demonstrated on cranial ultrasound in the early neonatal period (Anderson *et al.*, 2006).

The associations of microstructure in the cingulum with performance and eye–hand coordination sub-scores are novel in this young population. However, studies in adults have shown that mean diffusivity in the cingulum bilaterally and FA in the left cingulum are correlated to executive performance in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy), suggesting an association between executive dysfunction and white matter abnormality in this region (O'Sullivan *et al.*, 2005). Lesions in the anterior or posterior portions of this network are associated with deficits in working memory performance (Petrides and Milner, 1982) and reduced FA in the cingulum in schizophrenia is associated with attention and working memory deficits (Kubicki *et al.*, 2003).

Novel associations were also found between tissue microstructure in other white matter tracts of the limbic system including the fornix, anterior commissure and uncinate fasciculus and eye–hand coordination sub-scores. The fornix is the major limbic white matter pathway connecting the hippocampus and mamillary bodies and is implicated in both executive functioning and memory. Reduced FA values in the fornix in schizophrenia are associated with lower overall memory scores and poorer performance on tests of executive function, and in healthy adults higher FA values in the fornix are associated with higher scores in tests of verbal memory and recall (Nestor *et al.*, 2007). The uncinate fasciculus is the major fibre bundle connecting the temporal and frontal lobes, and the amygdala and uncus with the subcallosal region; it is thought that this pathway may be important in episodic memory and in emotions (Klinger and Gloor, 1960). The anterior commissure provides an inter-hemispheric connection for the temporal lobes, the orbitofrontal cortex and the amygdala. Whilst its role in cognition is not clear, electron microscopy in rhesus monkeys has demonstrated a correlation between the number of myelinated nerve fibres in this structure and cognitive performance (Sandell and Peters, 2003).

The correlation of poorer results in tests of eye–hand coordination and performance with reduced FA in neural systems associated with attention, executive function and working memory suggest that we may be identifying dysfunctions in information processing, and decision making regarding what action to perform and how to execute the action. In children with developmental coordination disorder, which manifests as difficulties with fine motor tasks in the absence of intellectual impairment, an inability to allocate attention for action has been identified, implying a relationship between attention deficits and eye–hand coordination problems (Wilmut *et al.*, 2007). An association between white matter abnormality in these brain regions and eye–hand coordination skills is supported by recent work in adults who suffered lead exposure, which demonstrated a correlation between reduced volume of white matter in several regions including the cingulum, hippocampus and corpus callosum and poor eye–hand coordination (Schwartz *et al.*, 2007).

In this relatively small group of infants, our overall DQ results were good for a population of children born at $\leqslant 32$ week's gestation with a mean gestation of 28 weeks. This is partly because we excluded any children with focal abnormality and none had a major motor deficit. It may also be in part due to the fact that the Griffiths test was last standardized in the years just preceding 1996, 10–12 years before the children in our study were tested and it is to be expected that the mean population DQ will have increased over this time (the Flynn effect) by three to four points (Flynn, 1999). However we have no evidence to suggest that the sub-quotient findings will change disproportionately. None of the children tested was having any specific training or therapy.

At this early stage of development testing children in different developmental domains is problematic as the skills they need for each sub-scale overlap. Whilst it may be expected that we did not find a relationship between the motor sub-scale and FA values in this group without major motor problems or focal lesions on their scans it is perhaps more surprising that there was no relationship with social or language development and FA values. This may be because these functions are less locally defined or more difficult to measure at this young age, or not developed sufficiently to assess differences between children. It may also reflect findings from longer-term follow-up studies showing that problems in these domains are not prominent in ex-preterm infants (Saigal and Doyle, 2008) in comparison to the well-documented later problems in fine motor (Rademaker *et al.*, 2004), attentional and cognitive functions (Bhutta *et al.*, 2002; Marlow *et al.*, 2005). The detection of a neural correlate to eye–hand coordination and performance scales at this young age supports the findings of others at later time points that problems in these domains are characteristic of this group.

Identifying specific neurodevelopmental impairments with objective imaging correlates suggests that DTI might be valuable in providing precise data on neurological prognosis for preterm infants, and FA measurements may be a qualified biomarker for studies to understand the mechanisms of injury or to assess the effectiveness of specific early interventions in this high-risk group of children.

Acknowledgements

We thank the families who took part in the study and our colleagues in the Neonatal Intensive Care Unit and Children's Ambulatory Unit at Hammersmith Hospital.

Funding

National Institute of Health Research Biomedical Research Centre Funding Scheme; National Institute of Health Research, post-doctoral award scheme, the Medical Research Council (UK); the Academy of Medical Sciences; the Health Foundation and Philips Medical Systems.

References

Anderson NG, Laurent I, Woodward LJ, Inder TE. Detection of impaired growth of the corpus callosum in premature infants. Pediatrics 2006; 118: 951–60.

Anjari M, Srinivasan L, Allsop JM, Hajnal JV, Rutherford MA, Edwards AD, et al. Diffusion tensor imaging with tract-based spatial statistics reveals local white matter abnormalities in preterm infants. Neuroimage 2007; 34: 896–904.

Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, Jacobsson P, et al. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol 2005; 47: 571–6.

Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. NMR Biomed 2002; 15: 435–55.

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002; 288: 728–37.

Boardman JP, Counsell SJ, Reuckert D, Kapellou O, Bhatia KK, Aljabar P, et al. Abnormal deep grey matter development following preterm birth detected using deformation-based morphometry. Neuromage 2006; 32: 70–80.

Cooke RW, Abernethy LJ. Cranial magnetic resonance imaging and school performance in very low birth weight infants in adolescence. Arch Dis Child Fetal Neonatal Ed. 1999; 81: F116–21.

Counsell SJ, Shen Y, Boardman JP, Larkman DJ, Kapellou O, Ward P, et al. Axial and radial diffusivity in preterm infants who have diffuse white matter changes on magnetic resonance imaging at term-equivalent age. Pediatrics 2006; 117: 376–86.

Dyet LE, Kennea N, Counsell SJ, Maalouf EF, Ajayi-Obe M, Duggan PJ, et al. The natural history of brain lesions in extremely preterm infants investigated by MR imaging. Pediatrics 2006; 118: 536–48.

Flynn JR. Searching for justice: the discovery of IQ gains over time. Am Psychol 1999; 54: 5–20.

Frisone M F, Mercuri E, Laroche S, Foglia C, Maalouf EF, Haataja L, et al. Prognostic value of the neurologic optimality score at 9 and 18 months in preterm infants born before 31 weeks' gestation. J Pediatr 2002; 140: 57–60.

Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999; 135: 153–61.

Huntley M. The Griffiths Mental Development Scales: from birth to 2 years. Association for Research in Infant and Child Development (ARICD) 1996.

Huppi PS, Maier PS, Zientara GP, Barnes PD, Jolesz FA, Volpe JJ. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. Pediatr Res 1998; 44: 584–90.

Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005; 115: 286–94.

Isaacs EB, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, et al. Hippocampal volume and everyday memory in children of very low birth weight. Pediatr Res 2000; 47: 713–20.

Kapellou O, Counsell SJ, Kennea NL, Dyet L, Saeed N, Stark J, et al. Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth. PLoS Med 2006; 3: e265.

Klingler J, Gloor P. The connections of the amygdala and of the anterior temporal cortex in the human brain. J Comp Neurol 1960; 115: 333–69.

Krishnan ML, Dyet LE, Boardman JP, Kapellou O, Allsop JM, Cowan F, et al. Relationship between white matter apparent diffusion coefficients in preterm infants at term equivalent age and developmental outcome at 2 years. Pediatrics 2007; 120: e604–9.

Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, et al. Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biol Psychiatry 2003; 54: 1171–80.

Langhoff-Roos J, Kesmodel U, Jacobsson B, Rasmussen S, Vogel I. Spontaneous preterm delivery in primiparous women at low risk in Denmark: population based study. Br Med J 2006; 332: 937–9.

Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986; 161: 401–7.

Maalouf EF, Duggan PJ, Rutherford MA, Counsell SJ, Fletcher AM, Battin M, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. J Pediatr 1999; 135: 351–7.

Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 2005; 352: 9–19.

Miller SP, Vigneron DB, Henry RG, Bohland MA, Ceppi-Cozzio C, Hoffman C, et al. Serial quantitative diffusion tensor MRI of the premature brain: development in newborns with and without injury. J Magn Reson Imaging 2002; 16: 621–2.

Moseley ME, Cohen Y, Kucharczyk J Mintorovitch J, Asgari HS, Wendland MF, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990; 176: 439–45.

Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. J Cogn Neurosci 2004; 16: 1227–33.

Nagy Z, Westerberg H, Skare S, Andersson LJ, Lilja A, Flodmark O, et al. Preterm children have disturbances of white matter at 11 years of age as shown by diffusion tensor imaging. Pediatr Res 2003; 54: 672–9.

Neil JJ, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, et al. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. Radiology 1998; 209: 57–66.

Nestor PG, Kubicki M, Kuroki N, Gurrera RJ, Niznikiewicz M, Shenton ME, et al. Episodic memory and neuroimaging of hippocampus and fornix in chronic schizophrenia. Psychiatry Res 2007; 15: 21–8.

Nosarti C, Rushe TM, Woodruff PW, Stewart AL, Rifkin L, Murray RM. Corpus callosum size and very preterm birth: relationship to neuropsychological outcome. Brain 2004; 127: 2080–9.

O'Sullivan M, Barrick TR, Morris RG, Clark CA, Markus HS. Damage within a network of white matter regions underlies executive dysfunction in CADASIL. Neurology 2005; 22: 1584–90.

Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, et al. Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. JAMA 2000; 284: 1939–47.

Petrides M, Milner B. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia 1982; 20: 249–62.

Rademaker KJ, Lam JN, van HI, Uiterwaal CS, Lieftink AF, Groenendaal F, et al. Larger corpus callosum size with better motor performance in prematurely born children. Semin Perinatol 2004; 28: 279–87.

Sandell JH, Peters A. Disrupted myelin and axonal loss in the anterior commissure of the aged rhesus monkey. J Comp Neurol 2003; 466: 14–30.

Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008; 371: 261–9.

Schwartz BS, Chen S, Caffo B, Stewart WF, Bolla KJ, Yousem D, et al. Relations of brain volumes with cognitive function in males 45 years and older with past lead exposure. NeuroImage 2007; 37: 633–41.

Skranes J, Vangberg TR, Kulseng, Indredavik MS, Evensen KA, Martinussen M, et al. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007; 130: 654–66.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004; 23 (Suppl 1): S208–19.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006; 31: 1487–505.

Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, et al. Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 1999; 353: 1653–57.

Vangberg TR, Skranes J, Dale AM, Martinussen M, Brubakk AM, Haraldseth O. Changes in white matter diffusion anisotropy in adolescents born prematurely. Neuroimage 2006; 32: 1538–48.

Volpe JJ. Cerebral white matter injury of the premature infant – more common than you think. Pediatrics 2003; 112: 176–80.

Wilmut K, Brown JH, Wann JP. Attention disengagement in children with developmental coordination disorder. Disabil Rehabil 2007; 29: 47–55.

Woodward LJ, Edgin JO, Thompson D, Inder TE. Object working memory deficits predicted by early brain injury and development in the preterm infant. Brain 2005; 128: 2578–87.

Yung A, Poon G, Qiu D, Chu J, Lam B, Leung C, et al. White matter volume and anisotropy in preterm children: a pilot study of neurocognitive correlates. Pediatr Res 2007; 61: 732–6.