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The Effect of Preterm Birth on Thalamic and Cortical Development

Gareth Ball1, James P. Boardman1,2, Daniel Rueckert3, Paul Aljabar3, Tomoki Arichi1,4, Nazakat Merchant1,4, Ioannis S. Gousias4, A. David Edwards1,4 and Serena J. Counsell1

1Centre for the Developing Brain, Imperial College London and MRC Clinical Sciences Centre, Hammersmith Hospital, London W12 0NN, UK, 2Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, UK, 3Biomedical Image Analysis Group, Department of Computing, Imperial College London, London SW7 2AZ, UK and 4Division of Neonatology, Imperial College Healthcare NHS Trust, London W12 0HS, UK

Preterm birth is a leading cause of cognitive impairment in childhood and is associated with cerebral gray and white matter abnormalities. Using multimodal image analysis, we tested the hypothesis that altered thalamic development is an important component of preterm brain injury and is associated with other macro- and microstructural alterations. T1- and T2-weighted magnetization images and 15-direction diffusion tensor images were acquired from 71 preterm infants at term-equivalent age. Deformation-based morphometry, Tract-Based Spatial Statistics, and tissue segmentation were combined for a nonsubjective whole-brain survey of the effect of prematurity on regional tissue volume and microstructure. Increasing prematurity was related to volume reduction in the thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale. After controlling for prematurity, reduced thalamic volume predicted: lower cortical volume; decreased volume in frontal and temporal lobes, including hippocampus, and to a lesser extent, parietal and occipital lobes; and reduced fractional anisotropy in the corticospinal tracts and corpus callosum. In the thalamus, reduced volume was associated with increased diffusivity. This demonstrates a significant effect of prematurity on thalamic development that is related to abnormalities in allied brain structures. This suggests that preterm delivery disrupts specific aspects of cerebral development, such as the thalamocortical system.

Keywords: brain development, deformation-based morphometry, DTI, cortex, TBSS, thalamus

Introduction

Preterm birth is rapidly emerging as a leading cause of neurodevelopmental impairment in childhood. With advances in neonatal intensive care, mortality has decreased considerably but there is a high prevalence of cognitive and behavioral deficits in up to 50% of surviving preterm infants in childhood (Marlow et al. 2005; Delobel-Ayoub et al. 2009). Understanding the neural substrates for impairment in this population is essential for designing mechanistic and therapeutic studies and may provide further insight into the development of systems that underlie human cognition.

Evidence from in vivo magnetic resonance imaging (MRI) studies has identified a number of cerebral abnormalities in preterm populations thought to reflect disturbances of key developmental processes during the neonatal period. The incidence of severe pathology such as periventricular leukomalacia (PVL) has declined (Horbar et al. 2002; Wilson-Costello et al. 2007); however, diffuse white matter changes in the absence of more obvious focal lesions are now the most common abnormality detected by conventional MR imaging. Diffusion tensor imaging (DTI) has revealed diffuse microstructural disturbances in the developing white matter that are dependent on the degree of prematurity at birth and correlated to short-term measures of neurodevelopmental outcome (Huppi et al. 1998; Counsell et al. 2006; Anjari et al. 2007; Krishnan et al. 2007; Ball et al. 2010). In addition, early systemic illness, in the form of chronic lung disease (CLD), has been shown to further exacerbate these alterations and impact negatively on outcome (Short et al. 2003; Anjari et al. 2007; Ball et al. 2010).

Morphometric MR studies have identified cortical disturbances developing before term-equivalent age (Ajayi-Obe et al. 2000; Inder et al. 2005; Kapellou et al. 2006), and widespread cerebral tissue loss is common in the presence of PVL and characterized pathologically by neuronal loss and gliosis (Inder et al. 2005; Pierson et al. 2007; Thompson et al. 2007; Ligam et al. 2009). These observations support the concept of an “encephalopathy of prematurity,” a complex of white and gray matter abnormalities that includes disruptions to the thalamocortical system with linked disturbances in the development and function of thalamic nuclei, topographically related cortical regions and connecting white matter tracts (Volpe 2009).

Indeed, even in the absence of severe focal white matter pathology, the subcortical gray matter and, in particular, the thalamus appears specifically vulnerable following preterm birth (Boardman et al. 2006; Srinivasan et al. 2007). Volumetric deficits in the thalamus also appear to be dependent on prematurity at birth and associated with poor functional outcome (Inder et al. 2005; Boardman et al. 2010). Transient developmental processes that underlie thalamocortical connectivity occur during a critical window for vulnerability following preterm birth and disruption of these processes may result in complex cerebral abnormalities (Allendoerfer and Shatz 1994; Volpe 2009; Kostovic and Judas 2010). Here, we examine the thalamocortical system of preterm infants at term-equivalent age, testing the hypothesis that tissue loss in the thalamus is associated with changes in the associated cortical gray matter and macro- and microstructural alterations in the cerebral white matter containing thalamocortical tracts.

Materials and Methods

Ethical permission for this study was granted by the Hammersmith and Queen Charlotte’s and Chelsea Hospital (QCCH) Research Ethics Committee. Written parental consent was obtained for each infant.
Subjects
Infants were recruited from the Neonatal Intensive Care Unit at QCCH. All infants born at less than 36 weeks gestational age (as defined by the last menstrual period) between March 2005 and October 2008 who successfully underwent $T_1$- and $T_2$-weighted MRI and 15-direction DTI acquisition at term-equivalent age were eligible for inclusion. Infants were excluded if cystic PVL or haemorrhagic parenchymal infarction was apparent on the term-equivalent MRI. Forty-eight infants (67.6%) had evidence of diffuse and excessive high signal intensity (DEHSI) on $T_2$-weighted scans; 8 infants (11.3%) had evidence of punctuate white matter lesions.

Seventy-four preterm infants (42 male) underwent successful imaging; 3 infants were removed prior to statistical analysis due to unsatisfactory alignment to the reference template. The final cohort of 71 did not differ from the original cohort in gestational age, age at scan, birth weight, or gender. The final cohort (41 male) had a median gestational age of 28 + 5 (range: 23 + 5 to 35 + 2) weeks, a median postmenstrual age at scan of 41 + 5 (38 + 1 to 44 + 4) weeks and median birth weight of 1.11 (0.63-2.87) kg. No infants received postnatal steroids. Across the whole cohort, the median (range) time spent receiving any form of respiratory support was 17 (0-116) days. Fifteen infants had CLD, defined by the need for respiratory support at 36 weeks postmenstrual age. All infants were included in a previously reported study optimizing Tract-Based Spatial Statistics (TBSS) for neonates and examining the effects of prematurity and CLD (Ball et al. 2010).

Imaging
MRI was performed on a Philips 3 T system (Philips Medical Systems, Netherlands) using an 8-channel phased array head coil. $T_1$-weighted MRI was acquired using: repetition time (TR): 17 ms; echo time (TE): 4.6 ms; flip angle 13°; slice thickness: 1.6 mm; field of view: 210 mm; matrix: 256 × 256 (voxel size: 0.82 × 0.82 × 0.8 mm). $T_2$-weighted fast-spin echo MRI was acquired using: TR: 8670 ms; TE: 160 ms; flip angle 90°; slice thickness 2 mm; field of view: 220 mm; matrix: 256 × 256 (voxel size: 0.86 × 0.86 × 1 mm). Single-shot echo planar DTI was acquired in 15 noncollinear directions (TR: 8000 ms; TE: 49 ms; slice thickness: 2 mm; field of view: 224 mm; matrix: 128 × 128 (voxel size: 1.75 × 1.75 × 2 mm); b value: 750 s/mm$^2$; SENSE factor of 2). All examinations were supervised by a pediatrician experienced in MRI procedures. Infants were sedated with oral chloral hydrate (25-50 mg/kg) prior to scanning and pulse oximetry, temperature and electrocardiography data were monitored throughout. Ear protection was used for each infant, comprising earplugs molded from a silicone-based putty (President Putty, Colteh Whaledent, Mahwah, NJ) placed in the external ear and neonatal earmuffs (MiniMuffs, Natus Medical Inc., San Carlos, CA).

Data Analysis

Thalamic Segmentation
The manual placement of regions of interest (ROI) on individual MR images can be subjective and manually intensive and does not easily allow for comparisons across large groups. To avoid this, a single bilateral thalamic mask was manually drawn on the final reference template according to anatomical borders previously described (Srinivasan et al. 2007) (Fig. 1B; for details of template construction, see Deformation-Based Morphometry). The high spatial correspondence between each $T_1$ image and the reference template following nonlinear registration precluded the need to manually place thalamic masks on individual $T_1$ images. Individual thalamic volume could be estimated by scaling the reference mask volume by the mean Jacobian determinant (a voxelwise measure of volume change between each image and the template, described below) calculated within the mask. To validate, manual thalamic segmentation was performed on $T_1$ images from 10 randomly selected infants, thalamic volumes measured manually and volumes estimated from the mean Jacobian were consistent (mean difference and limits of agreement = 0.29 ± 1.43; intraclass coefficient = 0.89; $P < 0.001$).

Cortical Segmentation
Cortical segmentation was performed on individual $T_2$ images using methods specifically optimized for neonatal tissue segmentation (for an example segmentation, see Fig. 1C). Images were initially segmented using an expectation-maximization segmentation method driven by age-specific coregistered tissue probability priors obtained from a 4D probabilistic neonatal atlas (Kulkosva-Murgasova et al. 2011). In addition, an automatic 3-step segmentation algorithm was used to remove mislabeled partial volume voxels at the interface of the gray matter and cerebrospinal fluid (Xue et al. 2007).

Deformation-Based Morphometry
Deformation based morphometry (DBM) does not require tissue segmentation or classification and can be used to localize regional variations in tissue volume. The key step is to achieve precise spatial correspondence between each subject’s image and a reference template through image registration. The output of each registration is a 3D deformation field representing transformations between each image and the final template. Voxelwise volume change induced by the transformation between each image and the template can be characterized by the determinant of the Jacobian operator applied to the transformation at any given point in the template space, referred to here as the Jacobian. Statistical groupwise analysis of the Jacobian reveals structural volume relative to the group template in an objective voxelwise manner (Ashburner et al. 1998; Rueckert et al. 2003).

After bias correction (FMRB’s Automated Segmentation Tool; FAST v4.1), each MR image was aligned to a chosen target image (gestational age = 28 + 5 weeks; postmenstrual age at scan = 42 + 0 weeks) using linear registration. A reference template was created by taking an intensity average of the aligned images. Each MR image was then aligned to the reference template using a high dimensional registration algorithm based on cubic B-splines (Rueckert et al. 1999, 2003) and averaged to form a second reference template. The nonlinear registration was carried out with successive control point point spacing of 20, 10, 5, and 2.5 mm using normalised mutual information information as the similarity metric and the bending energy of the deformation as the smoothness penalty (Gousias et al. 2010). A final set of registrations were performed with the second reference template as the target (Fig. 2). A qualitative evaluation of the alignment accuracy of the transformed images with the template was made before individual deformation fields were used to calculate volume changes. The average intensity template generated from the final set of registrations is shown in Figure 1A.

Voxelwise cross-subject statistical analysis of volume relative to the template, represented by the Jacobian, was performed with Randomise (v2.5) as implemented in FMRIB’s Software Library (Smith et al. 2004) (FSL v4.1; www.fmrib.ox.ac.uk/fsl). All statistical images were subject to false discovery rate (FDR) correction for multiple comparisons.

Tract-Based Spatial Statistics
DTI analysis was performed using FMRIB’s Diffusion Toolbox (FDT v2.0) and Tract-Based Spatial Statistics (Smith et al. 2006) (TBSS v1.2). From each data set, the tensor eigenvalues, $\lambda_1$, $\lambda_3$, and $\lambda_2$, describing the diffusion strength in the primary, secondary, and tertiary diffusion directions, and fractional anisotropy maps were calculated. Individual fractional anisotropy (FA) maps were averaged to form a common reference space and a mean FA skeleton, representing the center of all white matter tracts common to the group, was generated using a method optimized for neonatal DTI analysis (Ball et al. 2010). The calculated values of FA, axial diffusivity—the magnitude of $\lambda_1$, and radial diffusivity—the mean magnitude of $\lambda_2$ and $\lambda_3$ were then projected onto this skeleton. Nonparametric permutation-based statistical analysis was performed with Randomise; all diffusion statistics were subject to familywise error (FWE) correction for multiple comparisons following threshold-free cluster enhancement (Smith and Nichols 2009) and are shown at $P < 0.05$.

Statistical Analysis
Further statistical analysis with multiple linear regression was performed with SPSS 17.0 (SPSS Inc., Chicago, IL). In addition to explanatory variables of interest, gestational age at birth, postmenstrual
Results

Regional Brain Volume and Prematurity at Birth
Mean total cortical gray matter volume was 158 (± 26.6) ml. Both cortical gray matter volume and mean thalamic Jacobian (representing thalamic volume) were significantly associated with gestational age at birth, entered into the regression model with the age of each infant at scan (cortical volume: partial $r = 0.37$, $P = 0.002$; thalamic: partial $r = 0.40$, $P = 0.001$; Fig. 3).

DBM was used to locate other brain regions where tissue volume was associated with degree of prematurity at birth. Linear regression revealed significant localized associations between tissue volume (represented voxelwise by the Jacobian) and gestational age at birth (Fig. 4; FDR-corrected for multiple comparisons at $P < 0.01$; minimum $t$-statistic = 2.98). Increasing prematurity was associated with a bilateral pattern of reduced volume present at term-equivalent age and encompassing the anterior temporal lobes, including the hippocampus, the orbitofrontal lobe, and posterior cingulate cortex and extending into the centrum semiovale. Within the deep gray matter, the relationship was most prominent in the thalamus. In addition, discrete clusters were observed in the midbrain and cerebellum. DBM also revealed that increasing prematurity was associated with increasing extra-cerebral CSF, but this did not pass correction for multiple comparisons.

Thalamocortical Development after Preterm Birth
Cortical volume was significantly associated with mean thalamic Jacobian, entered into the regression model with total brain tissue volume (partial $r = 0.32$, $P = 0.007$; Fig. 3C). This association remained significant when also including gestational age at birth (partial $r = 0.31$, $P = 0.009$).

After correcting for the effects of prematurity and removing volume change due to individual differences in global brain scaling, DBM revealed significant volumetric covariance between the thalamus and subcortical cerebral tissue (Fig. 5; FDR-corrected $P < 0.001$, minimum $t$-statistic = 3.25). A bilateral pattern was observed comprising white and gray matter proximal to the thalamus and extending into the frontal and temporal lobes, including the hippocampus, through the centrum semiovale into the parietal lobe and, to a lesser extent, the occipital lobe. DBM also revealed significant localization of white and gray matter volume change in the thalamus and across the cerebral cortex.
extent, into periventricular white matter in the occipital lobes. This pattern remained highly significant when also covarying for total cortical volume (Supplementary Fig. 1).

In addition to the observed structural associations, TBSS was used to identify where white matter microstructure was associated with thalamic and cortical volume. Increasing thalamic volume at term-equivalent age was significantly associated with FA in the posterior limb of the internal capsule and corpus callosum (including the splenium) after correction for degree of prematurity at birth and the age of each infant when scanned (FWE-corrected for multiple comparison, \( P < 0.05 \); Fig. 6). Within these regions, linear regression showed that decreasing thalamic volume was independently associated with increasing radial diffusivity (partial \( r = -0.34, P = 0.004 \)) but not with axial diffusivity (partial \( r = 0.008 \)) when entered into a model with gestational age at birth and age at scan.

Cortical volume was significantly associated with FA in the posterior corpus callosum after correction for degree of prematurity at birth and age at scan (\( P < 0.05 \), Fig. 7). In these regions, only radial diffusivity was significantly associated with cortical volume (partial \( r = -0.29, P = 0.014 \); axial diffusivity: partial \( r = 0.15, P = 0.21 \)) independent of gestational age and age at scan. Both thalamic and cortical associations remained significant when also correcting for CLD status (Supplementary Fig. 2; CLD defined as requiring respiratory support at 36 weeks postmenstrual age). To investigate the interaction of thalamic and cortical associations with white matter microstructure, a secondary ROI analysis was performed. FA values were extracted from masks in the posterior limb of the internal capsule and posterior corpus callosum (Supplementary Fig. 3). In the internal capsule, FA was significantly associated with thalamic (partial \( r = 0.35, P = 0.003 \)) but not cortical volume (partial \( r = -0.13, P = 0.29 \)) when both metrics were entered into linear regression alongside gestational age and age at scan (Supplementary Fig. 3A). Conversely, FA in the posterior corpus callosum was significantly associated with cortical volume (partial \( r = 0.26, P = 0.034 \)) but not with thalamic volume (partial \( r = 0.07, P = 0.36 \); Supplementary Fig. 3B).

Finally, to determine how reduced thalamic volume is reflected by the underlying tissue microstructure, mean diffusivity (mean magnitude of \( \lambda_1, \lambda_2, \) and \( \lambda_3 \)) was extracted from each infant’s DTI using a thalamic mask transformed onto the DTI reference template. Linear regression revealed that smaller thalamic volume was associated with increased mean thalamic diffusivity when entered into a model with gestational age at birth, total brain volume, and cortical volume (Fig. 8; partial \( r = -0.395, P = 0.001 \)). TBSS analysis revealed that thalamic diffusivity was significantly associated with FA in the internal capsule, after correction for degree of prematurity, age at scan, cortical volume, and CLD status (Fig. 8B; FWE-corrected \( P < 0.05 \)).

**Discussion**

These data showed a significant effect of prematurity on thalamic volume related to specific abnormalities in allied brain structures. The effects of prematurity were far-reaching, with reductions in the volume of thalamus, hippocampus, orbitofrontal lobe, posterior cingulate cortex, and centrum semiovale that suggest preterm delivery disrupts specific aspects of cerebral development. However, after this general effect was accounted for, a pattern of structural covariance was observed between the thalamus and particular brain structures, notably in frontotemporal regions, cingulate gyrus, and hippocampus. The observed relation between reduced thalamic and total
Figure 4. Regional associations between brain tissue volume and prematurity at birth. Regions where tissue volume is significantly associated with gestational age at birth after correcting for the age of each infant at scan are shown in (A). Statistical images are corrected for multiple comparisons at $P < 0.01$ FDR-corrected (color bar indicates $t$-statistic). To illustrate this relationship, the Jacobian determinant, representing volume change relative to the reference template, at the site of the maximum $t$-statistic (red crosshairs; $t = 6.04$), was entered into a multiple linear regression with gestational age at birth and age at scan. The partial regression plot (B) shows the relationship between Jacobian and gestational age at birth.

Figure 5. Regional associations between brain tissue volume and thalamic volume at term-equivalent age. Regions where cerebral tissue volume significantly covaried with mean thalamic Jacobian (calculated within the region circled in red). Arrows indicate the hippocampi, statistical images are corrected for multiple comparisons at $P < 0.001$ FDR-corrected (color bar indicates $t$-statistic).
cerebral cortical volume together with abnormal thalamic and white matter microstructure suggests the hypothesis that these observations result at least in part from disrupted development of the thalamocortical system.

Previously, altered brain development at term-equivalent age has been detected in preterm infants (Volpe 2009). Studies using tissue segmentation reported that reduced cortical and deep gray matter volumes correlated to neurodevelopmental
Thalamic volume is therefore related to both the microstructure of the thalamic radiations, carrying projection fibers to the cortex, and the volume of the cortex itself. In turn, cortical volume is associated with the microstructure of interhemispheric corticocortical fibers. It is possible that tissue volume in the thalamus and cortex thus reflects thalamocortical connectivity and is dependent on the growth and integrity of connecting white matter tracts.

Reduced thalamocortical volume might also reflect reduced cell and axon numbers in component structures. The number of neurons in topographically connected thalamic and cortical regions is closely related (Stevens 2001) and a large body of histological evidence has determined that both thalamocortical and callosal corticocortical connections are established by term-equivalent age in humans and other primates (Kostovic and Rakic 1984; LaMantia and Rakic 1990; Kostovic and Jovanov-Milosevic 2006). This process can be interrupted by adverse events: cerebral irradiation in mid-to-late pregnancy leads to parallel neuronal loss in the thalamus and cerebral cortex and volume reduction in the subcortical white matter indicating the presence of shared developmental trajectories (Schindler et al. 2002; Selemon et al. 2005, 2009). We found reduced thalamic volume in association with increased mean thalamic diffusivity suggestive of larger extracellular space and compatible with reduced cell density (Beaulieu 2002) and reduced white matter anisotropy with increased radial diffusivity compatible with reduced axon density in associated white matter tracts. Decreased thalamic volume, increased thalamic diffusivity, and increased white matter radial diffusivity are together compatible with decreased cell numbers in the thalamocortical system.

Volpe (2009) argues that brain development in preterm infants is ultimately dependent on a combination of destructive and impaired maturational mechanisms. Here, by removing infants with severe focal lesions such as PVL, we have limited the potential impact of acquired destructive brain lesions on our observations; however, 67% of the cohort had some evidence of DEHSI, thought to reflect diffuse white matter injury possible due to ischemic or hypoxic pathways (Counsell et al. 2003, 2006). Defining normal white matter in the preterm population with conventional MRI is a subjective process; however, by using diffusion metrics such as FA and radial diffusivity (RD), we are able to perform an objective analysis of white matter integrity to capture more fully the spectrum of white matter abnormality present in this population. Additionally, converging evidence suggests that systemic illness in the neonatal period increases the risk of injury and adverse neurodevelopmental outcome (Miller and Ferriero 2009) and we have previously shown in this cohort that CLD is associated with decreased FA and increased RD in the cerebral white matter (Anjari et al. 2009; Ball et al. 2010). Factoring in the presence of CLD status, the pattern of microstructural covariance between the thalamus and the internal capsule and the cortex and corpus callosum remained, although the extent of the associations was reduced. This indicates that numerous injurious processes associated with preterm birth and systemic illness and mediated through inflammatory or excitotoxic

Figure 8. Thalamic diffusivity is associated with thalamic volume and FA in the internal capsule. Thalamic volume (estimated from the mean Jacobian) and mean thalamic diffusivity (estimated from a thalamic mask placed in the DTI reference space) were entered into a multiple linear regression model with gestational age at birth (GA), cortical volume, and total brain volume. The partial regression plot in (A) shows the significant association between thalamic volume and thalamic diffusivity. In (B), regions where FA was significantly associated with thalamic diffusivity are shown (FWE-corrected at P < 0.05), beyond any associations with GA, PMA, cortical volume, and CLD status.
pathways (Arai et al. 1995; Back et al. 2005; Bell et al. 2005; Robinson et al. 2006; Ligam et al. 2009) may potentiate the observed structural and microstructural covariations, possibly with subsequent downstream effects on thalamic volume and development of the overlying cortex (Volpe 2009), resulting in the gestation-dependent pattern of brain development described here. Further investigation during the early neonatal period and longitudinal follow-up of this cohort may help elucidate the nature and evolution of maldevelopment in white matter, deep gray matter, and cerebrum as a whole in this population.

It should be noted that the DBM analyses did not reveal significant associations in the cortex. This was not unexpected: DBM is highly sensitive to local volume change that is spatially consistent across the whole group and thus relies on precise spatial correspondence without reliance on tissue classification and spatial smoothing, however due to the rapid increases in cortical complexity during the neonatal period (Kapellou et al. 2006) and limitations in current image registration techniques for neonates, achieving precise correspondence in cortical regions remains difficult. By combining DBM with cortical segmentations in native image space, we were still able to capture information from the whole brain in this cohort.

In summary, we have shown that at term-equivalent age and in the absence of severe white matter injury, preterm infants show a detailed pattern of altered brain structure and microstructure that mirror changes seen in adolescent-ex-preterm infants and are compatible with disruption of thalamocortical development.

Supplementary Material
Supplementary material can be found at: http://www.ercor.oxfordjournals.org/

Notes
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