

Diminished regional brain growth is associated with impaired white matter microstructural development following premature birth

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Background

Preterm birth is a leading cause of cognitive impairment in childhood¹, and is associated with a spectrum of structural brain abnormalities²⁻⁵ but the nature and evolution of these altered developmental processes are poorly understood. Recent pathologic and *in vivo* imaging studies have focused attention on abnormal thalamic development in association with diffuse white matter injury as important components of preterm brain injury that relate to early measures of neurodevelopmental outcome^{5,6}. Here, using Deformation-Based Morphometry⁷ (DBM) and Tract-Based Spatial Statistics⁸ (TBSS) we performed analyses of brain development to show that thalamic and fronto-temporal lobar volumes are both related linearly to the degree of prematurity at birth, and we provide evidence that reduced thalamic volume is associated with specific microstructural alterations in developing white matter tracts.

Methods

71 preterm infants (median gestational age at birth = 28⁺⁵ weeks; range: 23⁺⁴ – 35⁺²) underwent 3-Tesla T1-weighted anatomical MRI (MP-RAGE) and 15-direction DTI acquisition at term-equivalent age. For DBM, individual T1-weighted images were aligned to a chosen target using rigid and affine 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 non-rigid registration. A second reference template was created by taking an intensity-average of the non-rigidly aligned images and a second iteration of non-rigid registrations to the final template was performed. Linear regression was used to determine brain regions where volume change, represented by the Jacobian determinant extracted from the three-dimensional deformation fields of the final set of registrations, was significantly associated with gestational age at birth. For TBSS, individual FA maps and tensor eigenvalues, λ_1 , λ_2 and λ_3 , were calculated from individual DTI datasets and aligned to a common reference space. The images were skeletonised and the calculated values of FA, axial diffusivity – the magnitude of λ_1 – and radial diffusivity – the mean magnitude of λ_2 and λ_3 were projected onto the mean skeleton. Linear regression was used to identify regions where thalamic volume, estimated from the mean Jacobian determinant within a thalamic mask, was associated with altered white matter microstructure.

Results

Figure 1 shows a widespread association between regional brain tissue volume and prematurity at birth (FDR-corrected, $p < 0.01$) in the following brain regions: anterior temporal lobes, including the hippocampus; the orbitofrontal lobe; posterior cingulate cortex; the centrum semiovale and the deep grey matter, including the thalamus. Thalamic volume was significantly associated with predominantly bilateral increases in FA in the corticospinal tracts, corpus callosum and cingulum after correction for both prematurity at birth and the age of each infant when scanned (FWE-corrected, $p < 0.05$; Figure 2). Within these regions, increasing thalamic volume was associated with radial diffusivity (partial $r = -0.339$, $p < 0.01$) but not with axial diffusivity.

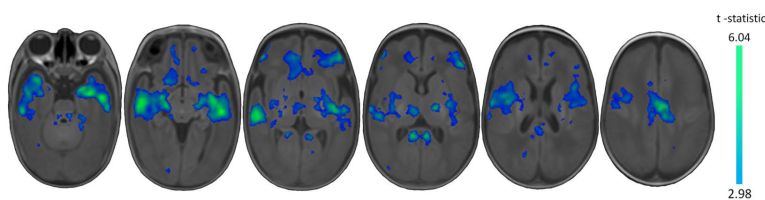
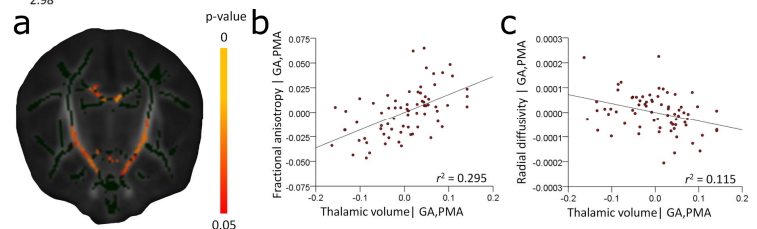


Figure 1: Regions where tissue volume is significantly associated with gestational age at birth after correcting for the age of each infant at scan ($p < 0.01$, FDR-corrected).

Figure 2: Regions where FA is significantly associated with thalamic volume (a), after correcting for prematurity at birth and age at imaging ($p < 0.05$, FWE-corrected). Partial correlation plots show the relationship between thalamic volume and FA (b) and RD (c) in those regions.



Conclusion

We show that growth of fronto-temporal white matter, the cingulate and the hippocampus, and subcortical structures including the thalamus is gestation dependent. This pattern closely mirrors correlates of preterm birth that mediate neurodevelopmental outcome in the adolescent brain⁹ and these findings may therefore be early markers of subsequent dysfunction. We confirm that diminished thalamic growth and microstructural alterations in major white matter tracts occur in parallel after premature birth, forming two major associated components of preterm brain injury and possibly representing downstream consequences of a common primary insult⁶.

References

1. Marlow, N. *et al. N. Engl. J. Med.* **352**, 9-19 (2005)
2. Huppi, P. S. *et al. Pediatr. Res.* **44**, 584-590 (1998)
3. Inder, T. E. *et al. Pediatrics* **115**, 286-294 (2005)
4. Counsell, S. J. *et al. Pediatrics* **117**, 376-386 (2006)
5. Boardman, J. P. *et al. Ann. Neurol.* **62**, 185-192 (2010)
6. Volpe, J. J. *Lancet Neurol.* **8**, 110-124 (2009)
7. Rueckert, D. *et al. Medical Imaging, IEEE Transactions on* **22**, 1014-1025 (2003)
8. Smith, S. M. *et al. Neuroimage* **31**, 1487-1505 (2006)
9. Nosarti, C. *et al. Brain* **131**, 205-217 (2008)