Investigating The Long-Term Effects Of Preterm Birth On Brain White Matter Using Tract-Based Spatial Statistics and Fractional Anisotropy data

Z. Nagy[1], S. Jbabdi[2], J. Andersson[3], S. Skare[4], and H. Lagercrantz[5]

[1]Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom, [2]FMRIB, University of Oxford, Oxford, United Kingdom, [3]FMRIB, Oxford University, Oxford, United Kingdom, [4]Lucas MRS/I Center, Department of Radiology, Stanford University, Stanford, United States, [5]Department of Woman and Child Health, Kaolinska Institute, Stockholm, Sweden

Introduction: With the introduction of neonatal intensive care units the survival of those infants born preterm increased dramatically. To investigate the long-term effects of preterm birth, several large cohort studies were initiated. It is now apparent that differences exist in neonatal care methods (1), which may have significant effects on the developmental outcome (2-3). The direct causes for these morphological and cognitive deficits have not yet been completely elucidated. However, it is generally accepted that the central nervous system and its supporting vasculature are vulnerable to injury during the period between the 22nd week of gestation and term and that the distressing extra uterine environment can be harmful. The Stockholm Neonatal Project (4) was started in order to investigate how the long-term outcome of individuals born preterm fits into the internationally reported spectrum.

Methods: Subjects: Between September 1988 and march 1993 infants born at or transferred to the Karolinska Hospital were included if the birth weight (BW) was ≤1500g and the gestational age (GA) was less than 37 weeks. Starting in April 2005 these individuals were invited in a random order and 74 ex-preterm and 69 term-born adolescents complied. They did not differ from the total available group with respect to gestational age, birth weight, sex distribution, the mother's age at birth, the mother's level of education or general cognitive development at 5 ½ years (5). This study was performed with the approval of the local ethics committee.

MRI data acquisition: All the participants underwent a cranial MR examination using a 1.5T GE scanner (Waukesha, WI, USA). Diffusion tensor imaging data was collected twice in 30 non-collinear directions with b = 1000 s/mm^2 and for reference images. The two sets differed in the phase encoding blip direction in order to estimate and remove susceptibility induced distortions. The acquisition was pulse triggered with TE=72ms, Flip angle=90º and voxel size= 1.96x1.96x3.0mm^3. A 3D SPGR anatomical image was also acquired. Pre-processing of MRI images: The two sets were first combined into a single set which was corrected for movement and eddy current distortions (6) as well as susceptibility distortions (7). This datset was used to estimate the diffusion tensor and from that to calculate the fractional anisotropy images (8) which were subsequently put through the tract-based spatial statistics pipeline (9). The T1-weighted images were segmented (10) and total white matter volume was estimated by integrating the WM segment images. Statistical analyses: Two sample t tests were used to compare the GMV of the groups assuming unequal variances, whereas cluster-level statistics were employed as implemented within the FSL software (www.fmrib.ox.co.uk).

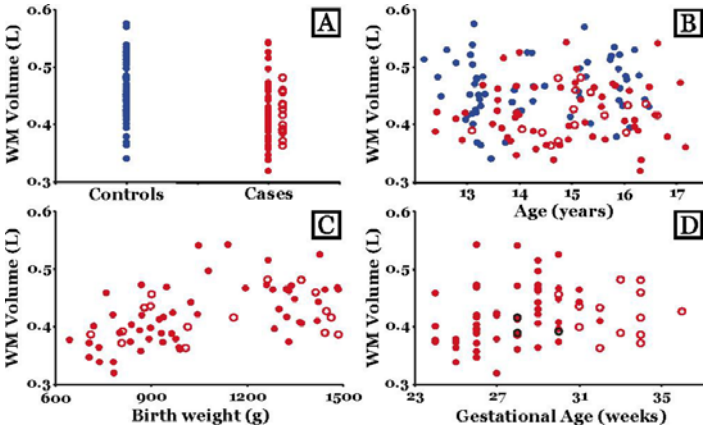

Figure 1 White matter volume vs age, birth weight and gestational age

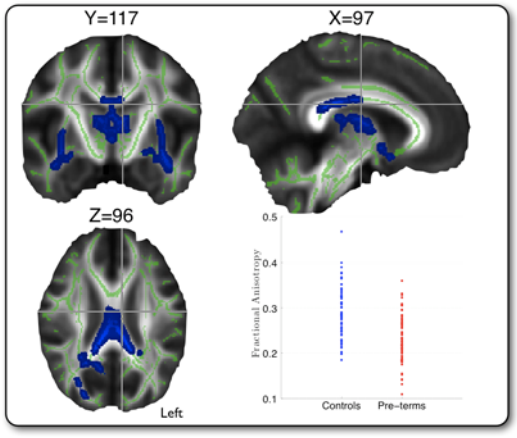

Figure 2 Results of the tract-based spatial statistics analysis

Results: We found a slight but significant reduction in total white matter volume of ex-preterm adolescents (Fig. 1A). As expected the white matter volume of individuals had direct relationship with the age of the individual (Fig. 1B) and was directly related to both birth weight (Fig. 1C) and gestational age (Fig. 1D). Voxel-wise comparisons revealed that ex-preterm adolescents had lower fractional anisotropy in the posterior corpus callosum, the fornix and bilaterally in the external capsules. Figure 3 displays the areas where fractional anisotropy was correlated with birth weight (top) and gestational age (bottom).

Discussion: We identified preterm birth as a risk factor for long-term grey matter development. However, it is notable that in Fig. 1A there is a large overlap between the groups and although the difference is statistically significant, biological significance may be debatable. Also note that, compared to similar studies previously published (11), (12) the extent injury to the brain, due to preterm birth was more moderate. This may be due to the minimally invasive neonatal care in Stockholm, and also to the set-up of social structure in Sweden in general where health care is free, unwanted pregnancies could be terminated and there was a near 100% attendance at antenatal clinics.

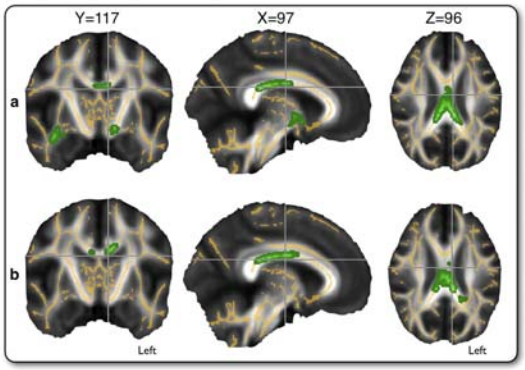

Figure 3 Fractional anisotropy vs BW and GA

References

1. Van Reempts P, et al. Pediatrics 2007;120(4):e815-e825.
2. Als H, et al. Pediatrics 2004;113(4):846-857.
3. Murphy BP, et al. Pediatrics 2001;107(2):217-221.
4. Katz-Salamon M, et al. Acta Paediatrica 1997;86(Suplement 419).
5. Bohm B, et al. Dev Med Child Neurol 2002;44(8):508-516.
6. Andersson JL, Skare S. Neuroimage 2002;16(1):177-199.
7. Andersson JL, Skare S, Ashburner J. Neuroimage 2003;20(2):870-888.
8. Basser PJ, Pierpaoli C. J Magn Reson B 1996;111(3):209-219.
9. Smith SM, et al. Neuroimage 2006;31(4):1487-1505.
10. Ashburner J, Friston KJ. Neuroimage 2005;26(3):839-851.
11. Vangberg TR, et al. Neuroimage 2006;32(4):1538-1548.
12. Constable RT, et al. Pediatrics 2008;121(2):306-316.