Investigating The Long-Term Effects Of Preterm Birth On Brain Volume Development Using Voxel-Based Morphometry Of MRI Data

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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 (2-4). 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 (5) 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 (6). 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). The protocol included a T1-weighted 3D SPGR image with TE=6ms, TR=24ms, Flip angle=30º, voxel size 0.98x0.98x1.5mm^3. Pre-processing of MRI images: Using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), the T1-weighted images were segmented (7). The grey matter segments were warped to the space of the average of all the subjects using DARTEL (8). The output images were scaled (i.e. modulated) by the Jacobians to preserve total volume irrespective of warping, re-sampled to 1.5mm isotropic voxels and smoothed with a 6mm full-width-at-half-maximum isotropic Gaussian kernel. The total GM volume was estimated by integrating the GM segment images. Statistical analyses: Two sample t tests were used to compare the GMV of the groups assuming unequal variances. The normalized and smoothed images were used in SPM5 in an exploratory analysis to compare the groups, using age and gender as covariates of no interest. In all cases p values of less than 0.05 were considered statistically significant. In voxel-wise testing correction was made for multiple comparisons by controlling the family-wise error rate.

Results: We found a slight but significant reduction in total grey matter volume of ex-preterm adolescents (Fig. 1A). As expected the grey matter volume of individuals had an inverse 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 an extensive set of bilateral regions where the ex-preterm adolescents had lower grey matter volume, including the temporal lobes, basal ganglia as well as the somatosensory, parietal, frontal and orbitofrontal cortices (Fig. 2). Figure 3 displays the same results on a 3D volume rendered segment of the mean white surface.

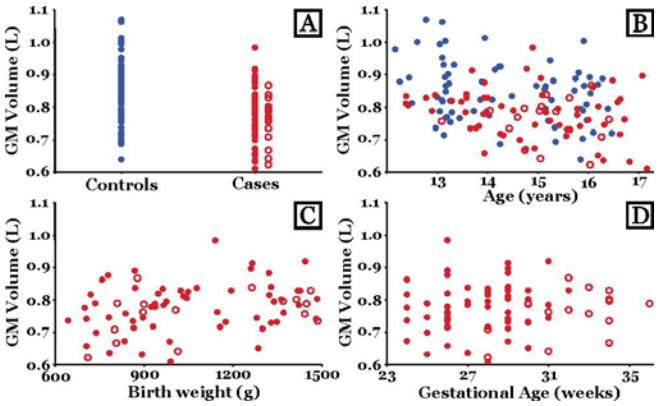

Figure 1 Grey matter volume vs age, birth weight and gestational age

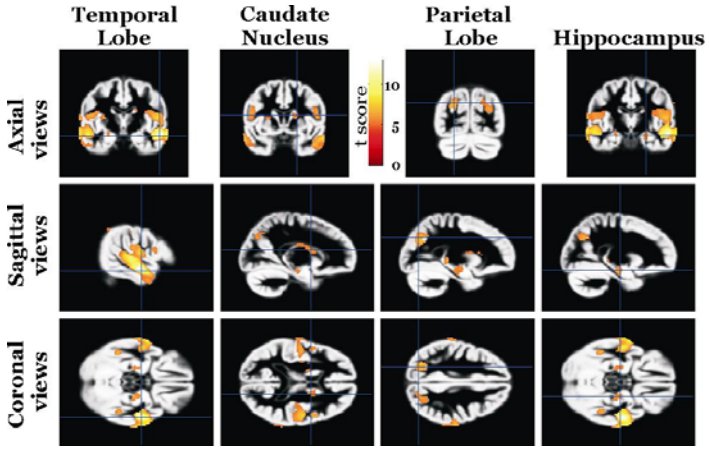

Figure 2 Results of the voxel-based morphometry analysis

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 if the brain volume is included as a covariate in the voxel-wise analysis the regions where statistical significance is reached is greatly reduced. Compared to similar studies previously published 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.

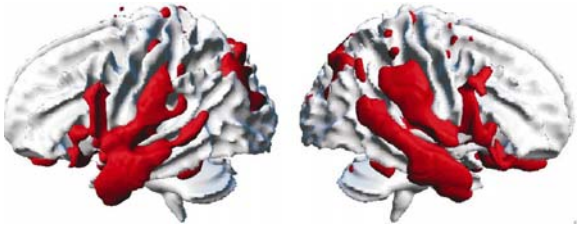

Figure 3 Volume rendered version of results in Figure 2

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