Gender differences in white matter microstructure in the adult brain revealed by Tract Based Spatial Statistics.

E. J. Hughes[1], D. J. Sharp[2], D. L. Hill[3], A. Wink[4], J. V. Hajnal[4], and S. J. Counsell[5]

[1]Robert Steiner MRI Unit, Hammersmith Hospital, Imperial College, London, England, United Kingdom, [2]Cognitive Neuroimaging Group, MRC Clinical sciences Centre, Imperial college, London, England, United Kingdom, [3]The London Bioscience Innovation Centre, IXICO ltd, London, England, [4]Hammersmith Hospital, Imperial College, Robert Steiner MRI Unit, London, England, United Kingdom, [5]Robert Steiner MRI Unit, Hammersmith Hospital, Imperial college, London, England, United Kingdom

Introduction. Recent computational magnetic resonance imaging studies have shown gender differences in the brain including in the central grey matter, cortical grey matter and white matter. Furthermore, diffusion tensor imaging studies (DTI) have found evidence for sexual dimorphism in a number of white matter tracts, with males having higher fractional anisotropy (FA) than females [1, 2]. However, the majority of these studies have used a region of interest approach of predetermined areas of the brain that mainly include the corpus callosum and the frontal lobe. The aim of this study was to assess whole brain white matter, in a large study group, in order to assess the extent of these microstructural differences using Tract Based Spatial Statistics (TBSS) [4].

Materials and methods. DTI, MP-RAGE and T2 turbo spin echo sequences were performed on ninety four healthy volunteers, (age range 20 – 74 years, mean age = 46.69 years), male n = 46 (mean age = 45) and female n = 48 (mean age =49) There was no significant difference in age between males and females, p=0.2. All subjects in the study were right handed and had normal radiological reports. Imaging was performed on a Philips Intera 3T system. The DTI scans were acquired using an echo planar imaging (EPI) sequence in 15 non-collinear directions with the following parameters: TR = 11591ms, TE = 51ms, voxel size: 1.75mm x 1.75mm x 2mm, 64 consecutive slices b-value = 1000 s/mm^2, and 1 image with no diffusion weighting (b=0 s/mm^2) and a SENSE factor of 2. Data analysis was performed using FSL [3]. Image artifacts 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 FDT. Voxel-wise statistical analysis of the FA data was carried out using TBSS implemented in FSL [4]. First, FA data were aligned into a common space using a non-linear registration algorithm. 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 $\geq$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 was then projected onto this skeleton. FA values in male and female brains were compared on voxel by voxel basis, corrected for age at scanning using TBSS. Results were corrected for multiple comparisons using threshold free cluster enhancement (TFCE) at $p < 0.01$.

Results FA values were significantly higher in the male brain in a number of regions (Figure 1). We did not observe higher FA values in the female brains in any region.

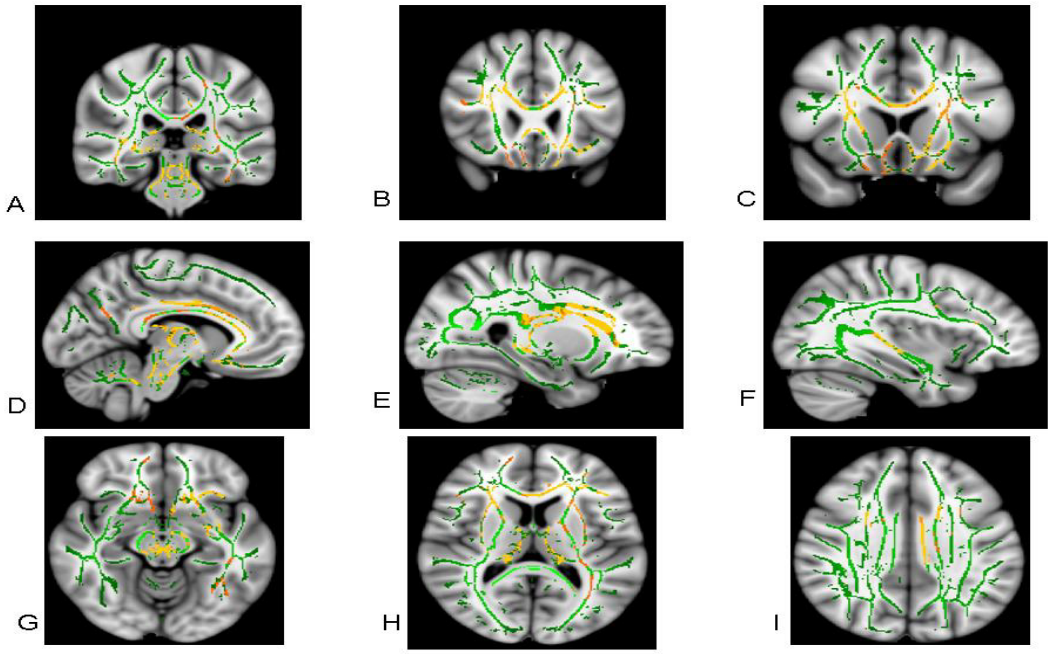

Figure 1 above shows regions where males have significantly higher FA than females (red-orange) overlaid on the mean FA skeleton (green) and include corpus callosum (B, C, D, H), left cingulate (D, I), corticospinal tracts (A), brainstem (G), bilateral anterior limb of the internal capsule (H), left posterior limb of the internal capsules (H), left retrolenticular part of the internal capsule (H), left optic radiation (H), external capsule (H) and fornix (D,H).

Conclusion The reasons for reported gender differences in the brain are not currently understood, and cannot be explained by the density of fibres [6] larger tract volumes in males, [8] or axonal coherence [7]. These differences may be due to differences in myelination [1] or perhaps may be due to the influence of sex hormones in brain development [5]. Using TBSS we have demonstrated extensive regions in the brain where the white matter microstructure differs between males and females, including a number of regions that have not been previously reported.

References (1) Westerhausen R et al, Neuroscience Letters 351 (99-102), 2003. **(2)** Hsu JL et al, NeuroImage 39 (566-577), 2007. **(3)** S.M. Smith et al, NeuroImage,23(S1):208-219,2004.**(4)** S.M. Smith et al, NeuroImage, 31:1487-1505, 2006. **(5)** Goldstein, J et al, CerebCortex, 11 (490-497) 2001. **(6)** Highly et al, Brain 122 (99-110), 1999. **(7)** Sullivan, EV et al NeuroReport 12 (99-104) 2001. **(8)** Aboitioz et al, Brain Res. 598 (143-153), 1992.