Combined fMRI and tractography reveal asymmetries in language pathways

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Introduction The combination of fMRI to identify cortical regions involved in specific functions and MR-tractography to visualise pathways connecting these regions offers an opportunity to study the relationship between brain structure and function. Most right handed people have left-sided dominance for language function[1] with the inferior frontal lobe involved in language production (Broca's area) and the posterior superior temporal gyrus involved in comprehension (Wernicke's area). We used fMRI and a probabilistic tractography algorithm extended to cope with the presence of crossing fibres within imaging voxels [2 3] to assess whether this asymmetry in function is reflected in the structural connections linking these regions.

Methods Studies were performed on a 1.5T General Electric Signa Horizon scanner with a standard quadrature head coil. 10 right-handed normal volunteers were studied. For the fMRI, gradient-echo echo-planar T2*-weighted images were acquired, providing blood oxygenation level dependent (BOLD) contrast. Each volume comprised 17 contiguous 4.6mm axial slices covering the frontal and temporal lobes (identical matrix and field of view to the DWI data -see below).TE was 40ms and TR 4.5s. A blocked experimental design was used with 30s task blocks alternating with 30s of rest over 5 ½ minutes. During the task blocks subjects were asked to silently generate different words starting with a particular letter. The images were analysed using SPM2. The imaging time series was realigned, normalized into standard anatomical space and smoothed with a Gaussian kernel of 10 mm FWHM. We produced a single contrast image for each subject corresponding to the main effect of word generation. At the second level of the random effects analysis, each subject's contrast image was entered into a one-sample *T* test to examine effects across the whole group. The group activation map, thresholded at $p<0.001$ (uncorrected) was then reverse normalised into the native space of each subject and these images were then used to define volumes of interest (VOIs) for initiating probabilistic fibre tracking. In each subject a VOI was created based on the peak fMRI activation in the left inferior frontal gyrus. As no significant activation was seen on the right a homotopic VOI of identical size was defined manually in the right frontal lobe.

The DWI acquisition used a single-shot spin-echo echo planar imaging (EPI) sequence, cardiac gated (triggering occurring every QRS complex) [4], with TE = 95s. A 96 x 96 acquisition matrix (128 x 128 reconstructed) and 22cm x 22cm field of view gave 2.3mm isotropic resolution on acquisition, reconstructed as 1.7 x 1.7 x 2.3mm. Acquisitions of 60 contiguous 2.3mm-thickness axial slices were obtained, covering the whole brain, with diffusion sensitizing gradients applied in each of 54 non-colinear directions (b value of 1148mm^2 s^{-1} (δ=34ms, Δ=40ms, gradient strength 22mTm^{-1})) along with 6 non-diffusion weighted (b=0) scans. The DWI acquisition time for a total of 3600 images was approximately 25 minutes (depending on the heart rate). The diffusion tensor eigenvalues λ_1, λ_2, λ_3 and eigenvectors ε_1, ε_2, ε_3 were calculated and fractional anisotropy (FA) maps were generated [5 6]. We used the method of Parker and Alexander [2 3] to enable tracking through fibre crossings. Voxels in which the single tensor fits the data poorly were identified using the spherical-harmonic voxel-classification algorithm of Alexander et al [7]. In these voxels a mixture of two Gaussian probability densities was fitted and the principal diffusion directions of the two diffusion tensors provided estimates of the orientations of the crossing fibres. In all other voxels a single tensor model was fitted.

We used the Probabilistic Index of Connectivity (PICo) algorithm extended to cope with crossing fibres [2 3] to track from the VOIs defined using fMRI. This adapts the commonly used streamline approach to exploit the uncertainty in one or more fibre orientations defined for each voxel. This uncertainty is defined using probability density functions (PDFs) constructed using simulations of the effect of realistic data noise on the result of the diffusion tensor mixture model [3]. The streamline process is repeated using Monte Carlo methods to generate maps of connection probability or confidence of connection from the chosen start regions. Each output connectivity map was normalised to standard space and then thresholded at probability values ranging from 0.001 to 0.1 to construct binary masks. The masks were averaged across the group indicating the degree of spatial variability and overlap of the identified connections [8]. The normalised tract volumes were calculated for the left and right tracts at each threshold and a paired T-test was used to compare the volumes over all the different thresholds.

Results fMRI activation was seen in the grey and white matter of the left inferior frontal gyrus. The group variability maps at a probability threshold of 0.005 for the volume of connection from the inferior frontal gyrus VOIs in the left and right hemispheres are shown in figure 1, demonstrating consistent bilateral connections extending posteriorly from Broca's area to Wernicke's area via the superior longitudinal fasiculus (SLF). An asymmetry in temporal lobe connections was demonstrated with greater connectivity extending to the superior and middle temporal gyrus on the left than on the right. The volume of connection was greater on the left than the right at each different threshold ($p<0.05$).

Conclusion Our results reveal an asymmetry in the language pathways with a larger connecting volume on the left and, in particular, greater connectivity to the temporal lobe on the left. These asymmetries reflect the lateralization of language function. The results, using a single functionally-defined VOI within each hemisphere are in keeping with a recent study which used two anatomically defined ROIs combined with non probabilistic tractography and showed greater temporal lobe connections on the left [9]. However, the strength of our study is in the use of probabilistic methods and the operator-independent definition of language-related tracking start VOIs. The ability of our tractography algorithm to cope with areas of high curvature and crossing fibres is demonstrated by the pattern of the left SLF and the lack of high probability false positive connections to the motor cortex. We hypothesise that it will be a useful tool for studying the effects of disease on language function and also in predicting post-operative deficits in patients undergoing neurosurgery.

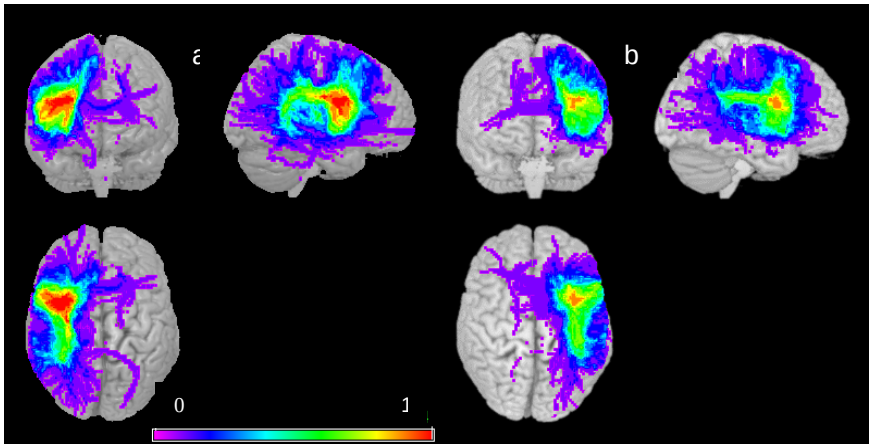

Figure 1. Variability maps of the left (a) and right (b) SLFs. The colour scale reflects the degree of overlap between subjects (0 indicates no subject had connection in a voxel; 1 indicates every subject had connection above the threshold in a voxel). The areas of low intensity reflect areas of high variability and represent non-specific connections.

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