

Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study

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Received 6 July 2005; revised 8 February 2006; accepted 7 March 2006
Available online 2 May 2006

Functional lateralization is a feature of human brain function, most apparent in the typical left-hemisphere specialization for language. A number of anatomical and imaging studies have examined whether structural asymmetries underlie this functional lateralization. We combined functional MRI (fMRI) and diffusion-weighted imaging (DWI) with tractography to study 10 healthy right-handed subjects. Three language fMRI paradigms were used to define language-related regions in inferior frontal and superior temporal regions. A probabilistic tractography technique was then employed to delineate the connections of these functionally defined regions. We demonstrated consistent connections between Broca's and Wernicke's areas along the superior longitudinal fasciculus bilaterally but more extensive fronto-temporal connectivity on the left than the right. Both tract volumes and mean fractional anisotropy (FA) were significantly greater on the left than the right. We also demonstrated a correlation between measures of structure and function, with subjects with more lateralized fMRI activation having a more highly lateralized mean FA of their connections. These structural asymmetries are in keeping with the lateralization of language function and indicate the major structural connections underlying this function.

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Introduction

The 19th century lesion-deficit model proposed by Broca and Wernicke recognized that language function depends upon both frontal and temporal cortical regions and the white matter tracts connecting them. In 1861, Broca reported a postmortem study of a patient with impaired speech production, finding an area of damage in the third frontal convolution of the left hemisphere (Broca, 1861). Subsequently, Wernicke reported a postmortem study of a patient who had an impairment of speech comprehension with damage to the left posterior superior temporal cortex (Wernicke, 1874). Wernicke's theory that damage to the connecting tracts would result in a specific language deficit, with intact speech comprehension and production but a deficit in repetition, was confirmed by the first reporting of a case of 'conduction aphasia' (Lichtheim, 1885).

Around the same time the dissections of Dejerine (1895) identified the trajectories of major white matter fiber bundles, and these pathways were subsequently visualized in three dimensions (Ludwig and Klinger, 1956). The superior longitudinal or arcuate fasciculus (SLF), a long association tract connecting frontal, parietal, and temporal cortex, was seen to originate in the inferior and middle frontal gyri, projecting posteriorly before arching around the insula into the temporal lobe. Lesions causing conduction aphasias typically lie in the inferior parietal cortex and therefore cause an interruption of these fibers as they pass between Broca's and Wernicke's area.

The lateralization of language function is a striking feature of human brain function and one that was recognized by both Broca and Wernicke. Two recent functional magnetic resonance imaging (fMRI) studies have demonstrated 94% (Springer et al., 1999) and 96% (Pujol et al., 1999) of right-handed subjects to be left

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Available online on ScienceDirect (www.sciencedirect.com).

hemisphere dominant for language function. These findings are in keeping with studies of previously normal patients with aphasias secondary to stroke (Geschwind, 1970) and epilepsy patients who did not have early brain injuries (Rasmussen and Milner, 1977). Greater atypical (bilateral and right-hemisphere) dominance is seen in left-handed subjects (Pujol et al., 1999) and in those with early left-hemisphere lesions (Adcock et al., 2003; Rasmussen and Milner, 1977; Springer et al., 1999).

An important question is the extent to which structural differences between left and right hemispheres underlie the lateralization of function, and whether this structural lateralization reflects the degree of functional lateralization from subject to subject. One brain region where asymmetry is evident is the upper surface of the temporal lobe adjacent to the sylvian fissure. In his original description of the anterior transverse gyrus (Heschl's gyrus), Heschl noted asymmetries in cortical folding (Galaburda et al., 1978a), and the area of superior temporal cortex posterior to this, the planum temporale, has also been demonstrated to be larger on the left than the right (Geschwind and Levitsky, 1968; Habib et al., 1995). This macroscopic asymmetry was reflected at the cellular level in the greater extent of the cytoarchitectonic area Tpt (temporoparietal cortex) on the left side (Galaburda et al., 1978b). More recently, volumetric MRI studies (Barrick et al., 2005; Pujol et al., 2002) and voxel-based morphometry (Good et al., 2001) have revealed white matter asymmetries in temporal and frontal lobes.

A non-invasive method of studying pathways of anatomical connectivity in vivo is magnetic resonance imaging (MRI) tractography, a technique derived from diffusion-weighted imaging. Diffusion-weighted imaging (DWI) is an MRI technique that evaluates brain structure through the three-dimensional measurement of water molecules' diffusion in tissue. Obstructions in the path of the molecules such as cell membranes affect the measured diffusion, an effect that is highly directional in white matter fibers. Via the use of the diffusion tensor and other methods the degree of diffusion (diffusivity), the directionality of the motion (anisotropy) and the principal orientation(s) of diffusion for each voxel (Jansons and Alexander, 2003; Pierpaoli et al., 1996; Pierpaoli and Basser, 1996; Tournier et al., 2004; Tuch et al., 2002, 2003; Tuch, 2004) may be calculated. This information can be used to evaluate connectivity between voxels and to generate streamlines corresponding to estimated fiber trajectories (Basser et al., 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Parker et al., 2002a,b; Poupon et al., 2000). Newer probabilistic tractography algorithms adapt the commonly used streamline approach by incorporating the uncertainty in the orientation of the principal direction of diffusion defined for each voxel to generate maps of probability of connection to chosen start points (Behrens et al., 2003a,b; Lazar and Alexander, 2005; Parker et al., 2003; Parker and Alexander, 2003).

A limitation of tractography algorithms has been their failure to take into account the presence of crossing fiber bundles. Recent developments have allowed the estimation of crossing fibers within voxels (Jansons and Alexander, 2003; Tournier et al., 2004; Tuch et al., 2002; Tuch, 2004). This is of particular importance when studying the SLF where it crosses the corona radiata.

Two recent studies have used tractography to study the connections of Broca's and Wernicke's areas (Catani et al., 2005; Parker et al., 2005), using anatomical guidelines to define starting points for fiber tracking. While both provide interesting new insights into the course of the SLF, both used a two volume-of-interest approach, whereby the analysis is constrained

to only include pathways passing through both regions. In addition, manual definition of starting regions may be prone to observer bias.

The combination of fMRI to identify cortical regions involved in specific functions and MR tractography to visualize pathways connecting these regions offers an opportunity to study the relationship between brain structure and function by providing a selective tracing of connectivity within a behaviorally characterized network (Mesulam, 2005). The use of fMRI-derived starting points also minimizes observer bias. This combination has previously been used to investigate the motor (Guye et al., 2003; Johansen-Berg et al., 2005) and visual (Toosy et al., 2004) systems.

In this study, we use these two imaging techniques to examine connectivity between functionally defined language areas in frontal and temporal lobes and test the hypothesis that in the functionally dominant left hemisphere, there would be stronger connections between language areas than between equivalent areas in the right hemisphere. We also aimed to extend the findings of previous studies by looking for a correlation between subjects' degree of functional asymmetry and the lateralization of the structural connections seen. If the pattern of structural connections truly reflected the underlying function, then we would expect those subjects with more lateralized language function to have more lateralized structural connections.

Materials and methods

Subjects

We studied 10 right-handed native English-speaking healthy volunteers with no history of neurological or psychiatric disease. Handedness was determined using the Edinburgh Hand Preference Inventory (Oldfield, 1971). The age range was 23–50 years (median 29.5). The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee and informed written consent was obtained from all subjects.

MR data acquisition

MRI studies were performed on a 1.5 T General Electric Signa Horizon scanner. Standard imaging gradients with a maximum strength of 22 mTm^{-1} and slew rate $120 \text{ Tm}^{-1} \text{ s}^{-1}$ were used. All data were acquired using a standard quadrature birdcage head coil for both RF transmission and reception.

Functional MRI

For the language tasks, gradient-echo echo-planar T2*-weighted images were acquired, providing blood oxygenation level-dependent (BOLD) contrast. Each volume comprised 17 contiguous 4.6 mm axial slices, with a 22 cm field of view and 96×96 acquisition matrix, reconstructed as a 128×128 matrix giving an in-plane voxel size of $1.7 \text{ mm} \times 1.7 \text{ mm}$. TE was 40 ms and TR 4.5 s. The field of view was positioned to maximize coverage of the frontal and temporal lobes. A single volume EPI was acquired with similar parameters and equal sensitivity to geometric distortions but a longer TR (Boulby et al., 2004). This allowed whole-brain coverage and was used as an anatomical reference and to aid spatial normalization.

Each subject performed three language fMRI experiments: verbal fluency, verb generation and reading comprehension. These paradigms consisted of a blocked experimental design with 30 s task blocks alternating with 30 s of rest over 5½ min. During the verbal fluency task block, subjects were asked to silently generate different words starting with a particular letter presented visually. The rest block consisted of visual fixation on a crosshair. During the verb generation task, concrete nouns were visually presented every 3 s in blocks of 10 nouns. Subjects were instructed to covertly generate verbs from the nouns during the task block and to silently repeat the nouns during the rest block. These paradigms were used to identify anterior language regions in the inferior and middle frontal gyri (Liegeois et al., 2004; Woermann et al., 2003).

During the reading comprehension activation condition, subjects silently read 9-word sentences covering a range of different syntactic structures and semantic content. No explicit task was required during scanning in order to avoid inducing additional executive processes. In the baseline condition, subjects attentively viewed 9-word sentences after all the letters were transformed into false fonts. This baseline controlled for visual input but not lexical, semantic, or syntactic content. The paradigm therefore maximized our chances of seeing reading related activation at any level of the reading system. Blocks of six sentences were interleaved with blocks of six false font sentences. Sentences and false fonts were presented one word at a time at a fixed rate (word duration, 500 ms; sentence duration, 5000 ms; block length, 30 s). This serial presentation mode was used to control for visual input, eye movements and to equate the subjects' reading pace. This paradigm was designed to identify posterior language regions in the superior and middle temporal gyri (Gaillard, 2004).

The data were analyzed with statistical parametric mapping (using SPM2 software from the Wellcome Department of Imaging Neuroscience, London; <http://www.fil.ion.ucl.ac.uk/spm>). Scans from each subject were realigned using the first as a reference, spatially normalized (using the whole brain EPI) (Friston et al., 1995) into standard space (Talairach and Tournoux, 1988), resampled to $3 \times 3 \times 3$ mm³ voxels and spatially smoothed with a Gaussian kernel of 10-mm FWHM. The time series in each voxel was high pass filtered with a cutoff of 1/128 Hz. A two-level random effects analysis was employed.

At the first level, condition-specific effects for each subject were estimated according to the general linear model (Friston et al., 1995). Regressors of interest were formed for each task by creating boxcar functions of task against rest. Parameter estimates for these regressors were then calculated for each voxel. Three contrast images were produced for each subject, corresponding to the main effects of verbal fluency, verb generation, and reading comprehension against the control conditions. All these images were used for the second-level analysis.

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. This was performed for the main effects of verbal fluency, verb generation, and reading comprehension. The group activation maps were thresholded at $P < 0.001$ (uncorrected) and reverse-normalized into each individual's native space. These reverse-normalized (native space) group fMRI activation maps were used to define volumes of interest (VOIs) for initiating probabilistic fiber tracking. A total of four VOIs were defined for each subject based on the fMRI activation maps, one each in the left and right inferior frontal gyri and left and right superior temporal

gyri. These were created by drawing over selected areas of fMRI activation (see Results for details) on consecutive brain slices, using MRICro (<http://www.psychology.nottingham.ac.uk>), and we specified that each VOI was of identical volume, comprising of 125 voxels.

Diffusion tensor imaging

The DWI acquisition sequence was a single-shot spin-echo echo planar imaging (EPI) sequence, cardiac gated (triggering occurring every QRS complex) (Wheeler-Kingshott et al., 2002), with TE = 95 ms. The acquisition matrix (96×96 , 128×128 reconstructed), field of view ($22 \text{ cm} \times 22 \text{ cm}$), and in-plane resolution on reconstruction ($1.7 \text{ mm} \times 1.7 \text{ mm}$) were identical to the fMRI data. Acquisitions of 60 contiguous 2.3-mm-thickness axial slices were obtained, covering the whole brain, with diffusion sensitizing gradients applied in each of 54 non-collinear directions (maximum *b* value of $1148 \text{ mm}^2 \text{ s}^{-1}$ ($\delta = 34 \text{ ms}$, $\Delta = 40 \text{ ms}$, using full gradient strength of 22 mTm^{-1})) along with 6 non-diffusion-weighted ($b = 0$) scans. The DWI acquisition time for a total of 3600 images was approximately 25 min (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 (Pierpaoli et al., 1996; Pierpaoli and Basser, 1996). We also used the method of Parker et al. (2003); Parker and Alexander (2003) to reduce fiber orientation ambiguities in voxels containing fiber crossings. Voxels in which the single tensor fitted the data poorly were identified using the spherical-harmonic voxel classification algorithm of Alexander et al. (2002). 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 fibers (Tuch et al., 2002). In all other voxels, a single tensor model was fitted.

We used the Probabilistic Index of Connectivity (PICo) algorithm extended to cope with crossing fibers (Parker et al., 2003; Parker and Alexander, 2003) to track from the functionally defined VOIs. This algorithm adapts the commonly used streamline approach to exploit the uncertainty due to noise in one or more fiber 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 fiber directions obtained from the mixture model (Parker and Alexander, 2003). 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 normalized to standard space and then thresholded at probability values ranging from 0.002 to 0.2 to construct binary masks. The masks were averaged across the group, to produce variability (or commonality) maps. These indicated the degree of spatial variability and overlap of the identified connections (Ciccarelli et al., 2003; Parker et al., 2005). A voxel commonality value *C* of 1.0 indicates that each individual had a connection identified in this voxel while *C* of 0.0 indicates that none of them did (Parker et al., 2005).

Tract volumes

For the commonality maps shown, we calculated connecting volumes $V(C)$ at different values of *C* to show the volume in standard space occupied by voxels above the commonality

threshold C . Finally, a lateralization index LI was calculated to assess lateralization of the connected volumes between hemispheres;

$$LI(C) = (V(C)_{\text{left}} - V(C)_{\text{right}}) / (V(C)_{\text{left}} + V(C)_{\text{right}})$$

where $V(C)_{\text{left}}$ and $V(C)_{\text{right}}$ are the tract volumes in cubic centimeter above a threshold value of C in the left and right hemispheres, respectively (Parker et al., 2005). No specific consideration was made for interhemispheric tracts.

The normalized tract volumes were also calculated for the left and right tracts of every subject at each probability threshold (Toosy et al., 2004). From these, a mean volume of left and right tracts was obtained for each threshold and a paired t test was used to compare the volumes.

Mean fractional anisotropy (FA)

For each probability threshold, the mean FA of the connected volume in native space was calculated for the left and right tracts. These were calculated by multiplying the binary masks with that subject's fractional anisotropy images and calculating the mean intensity value of the voxels isolated at each threshold. From these, a mean FA value of left and right tracts was obtained for each threshold, and a paired t test was used to compare these.

Correlations between structure and function

In order to investigate structure–function relationships in this group, we tested for correlations between the lateralization of fMRI activation and of the lateralization of the derived connections. For the fMRI, we calculated the mean activation within 20 mm radius spheres based on the peak activations in the left frontal and bilateral temporal lobe, along with a homotopic volume in the right frontal lobe, and calculated left minus right activation for each subject. For the tractography, we calculated lateralization indices as before to assess lateralization of both mean FA and connecting volumes between left and right-sided tracts. We calculated the Pearson's correlation coefficient to test our hypothesis that there would be a correlation between the two values, with subjects with greater functional lateralization also having more left-lateralized connections.

SPM regression analysis

Finally, each subject's fMRI contrast image was entered into a SPM2 simple regression model with the mean FA of the left-

sided tracts as a covariate. This allowed us to look at a voxel level for regions showing correlation between fMRI activation and the mean FA of the connections of language-related areas (Toosy et al., 2004). The resulting SPM maps were thresholded at $P < 0.001$.

Results

fMRI

Verbal fluency and verb generation were associated with areas of activation in the left inferior frontal gyrus, left middle frontal gyrus, and left insula (Table 1, Figs. 1A and B). Reading comprehension was associated with areas of activation bilaterally in the superior temporal gyri, adjacent to the superior temporal sulci (Fig. 1C) as well as a further area in the left posterior superior temporal gyrus (Fig. 1D). From these areas of activation, we created four VOIs for initiating fiber tracking (Fig. 1E). One was placed in the left inferior frontal gyrus and corresponded to an area of fMRI activation seen for both the verbal fluency and verb generation paradigms. As no significant activation was seen in this region on the right, a homotopic VOI of identical size was manually defined using MRICro. A further two functionally defined VOIs of identical size were placed bilaterally in the superior temporal gyri adjacent to the superior temporal sulci. These corresponded to the areas of bilateral activation seen during the reading comprehension task.

Tract volumes

As the PICO connection probability threshold increased, the tract volumes and the variability decreased, as the core tracts were increasingly identified. Tract volume was significantly greater on the left than the right for both pairs of VOIs across all different thresholds ($P < 0.05$) (Figs. 2A and B).

Mean fractional anisotropy (FA)

Increasing the PICO connection probability threshold had no significant effect on the overall mean FA of the combined left and right tracts. For the frontal VOIs, the mean FA was significantly greater on the left than the right ($P < 0.05$) across

Table 1
Activation peaks for all fMRI effects of interest

Contrast	Figure	MNI coordinates	Z score	Region
Verbal fluency	Fig. 1A	−44, 2, 24	4.28	Left inferior frontal gyrus
		−32, 26, −4	4.49	Left inferior frontal gyrus
		−38, 18, 10	4.31	Left insula
Verb generation	Fig. 1B	−44, 2, 24	5.56*	Left inferior frontal gyrus
		−44, 30, 22	5.32*	Left middle frontal gyrus
		−38, 22, 2	5.52*	Left insula
Reading comprehension	Fig. 1C	−44, −56, 12	4.99*	Left posterior superior temporal gyrus
		−52, −26, −6	4.63	Left superior temporal gyrus
		48, 26, −4	3.53	Right superior temporal gyrus
Regression analysis: word generation and mean FA	Fig. 6A	−56, −40, 22	4.26	Left supramarginal gyrus
Regression analysis: reading and mean FA	Fig. 6B	−36, 12, 20	3.08	Left inferior frontal gyrus

For each effect, the Montreal Neurological Institute (MNI) coordinate, Z score, anatomical location and relevant figure are given.

* $P < 0.05$ corrected for multiple comparisons.

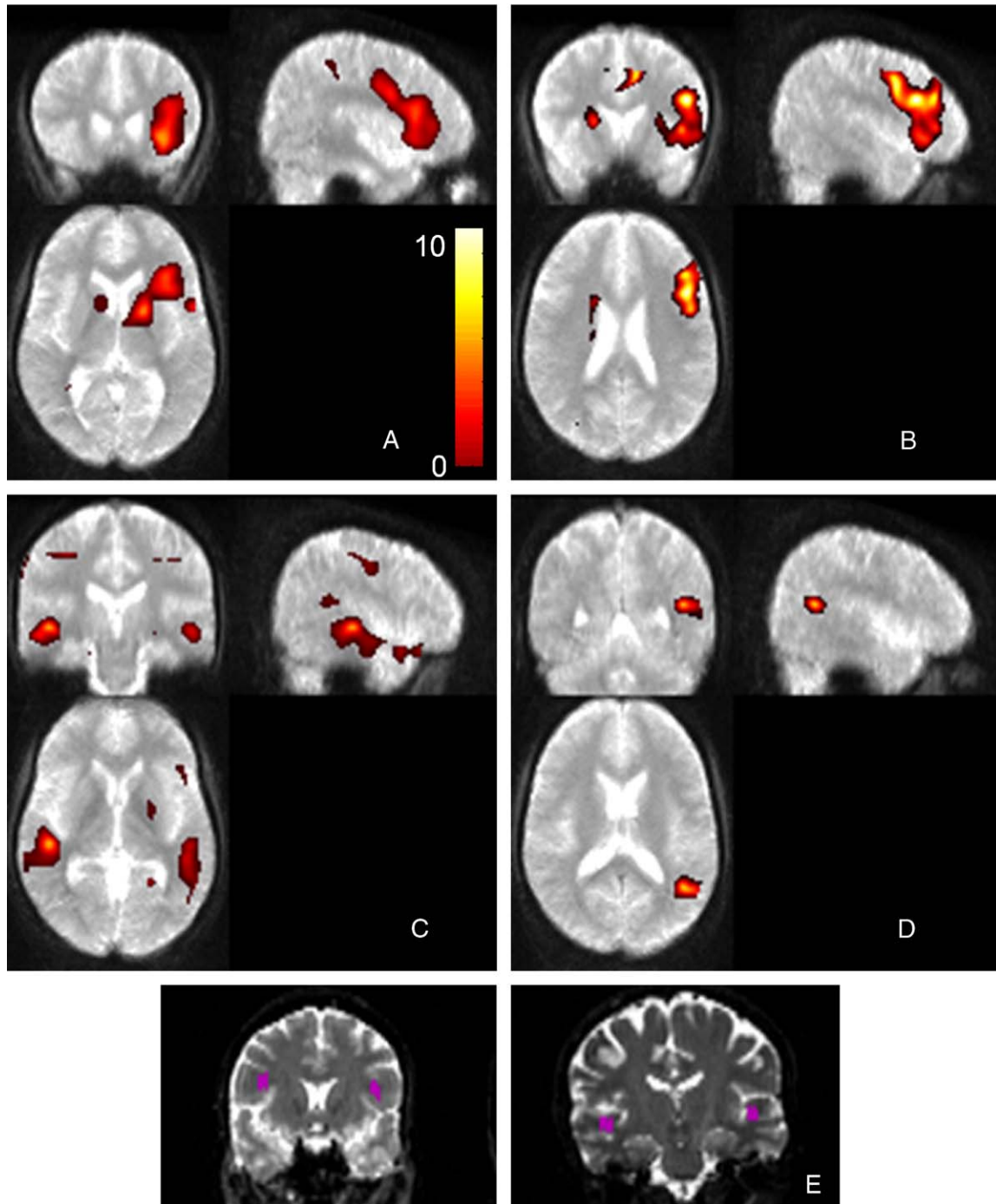


Fig. 1. fMRI results: main effects of the three language paradigms. Significant regions (threshold here and all subsequent figures $P < 0.001$) are superimposed onto the normalized mean EPI image from all 10 subjects. The left of the brain is displayed on the right of the image. Radiological viewing convention is used and the color bar indicates T scores. (A) Verbal fluency, left inferior frontal gyrus activation. (B) Verb generation, left inferior frontal gyrus activation. (C) Reading comprehension, activation bilaterally in the superior temporal gyri, adjacent to the superior temporal sulci. (D) Reading comprehension left posterior superior temporal gyrus activation. (E) Examples from a single subject of the four VOIs defined for initiation of fiber tracking (coronal views). The VOIs are located in bilateral inferior frontal gyri (left) and bilateral superior temporal gyri (right). VOIs are overlaid on that subject's non-diffusion-weighted $b = 0$ image in native space.

all different thresholds (Fig. 2C). For the temporal VOIs, there was no significant overall difference between left and right ($P = 0.06$) (Fig. 2D). For both VOIs, it can be seen however that the degree of left lateralization in mean FA value was greater at higher PICO thresholds (Figs. 2C and D).

Group variability maps

The group variability maps (at a probability threshold of 0.05) for the volumes of connection from both pairs of VOIs are shown in Figs. 3 and 4. The color scale indicates the degree of overlap

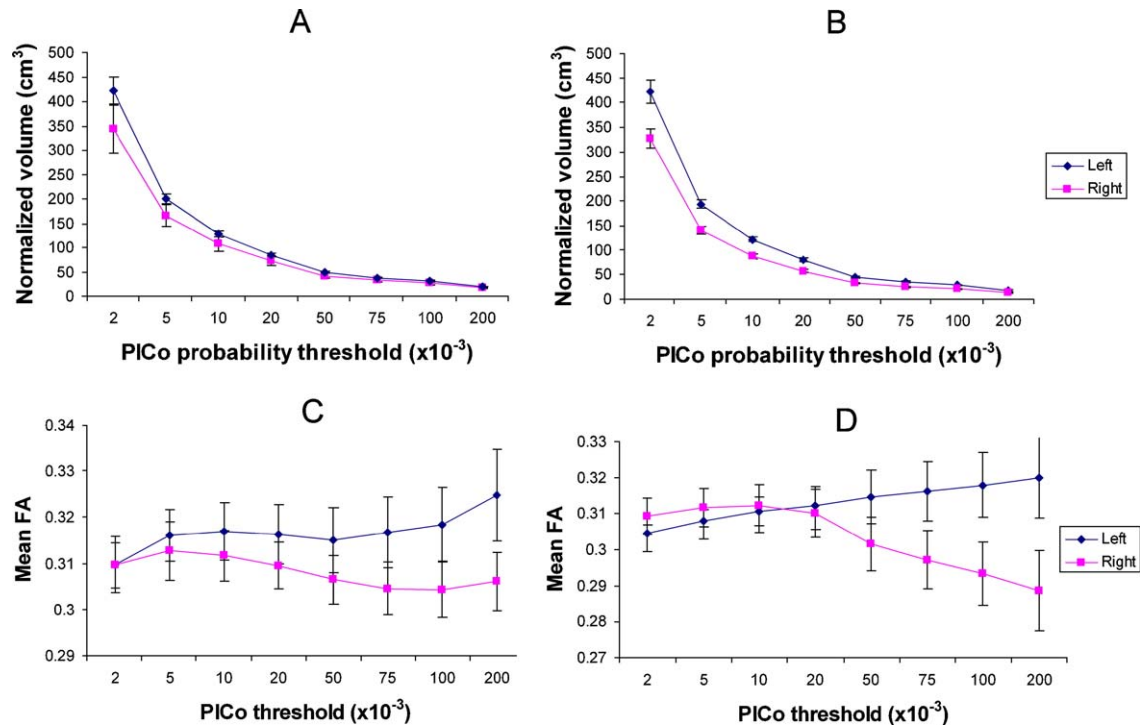


Fig. 2. Tract volumes (after normalization) as a function of PICo threshold (threshold range 0.002 to 0.2) for connections from frontal (A) and temporal (B) VOIs (\pm SE). Note greater tract volumes on the left than the right over all thresholds for both sets of connections. Mean FA as a function of PICo threshold (threshold range 0.002 to 0.2) for connections from frontal (C) and temporal (D) VOIs (\pm SE). Note the difference in mean FA was more marked at higher thresholds with higher values on the left than the right.

among subjects; for example, a value of 1 (pure red) represents 100% subject overlap (i.e., every subject's identified tract contains the voxel in question). These images show the maximum intensity of the connection patterns in each plane of view as a brain surface rendering.

The group variability maps for the volumes of connection from the left and right frontal VOIs demonstrated consistent bilateral connections extending posteriorly from Broca's to Wernicke's area via the superior longitudinal fasciculus (SLF) (Fig. 3). A clear qualitative difference was seen between the left and right maps with respect to the temporal lobe connections, with greater connectivity to the left superior and middle temporal gyri than the right. Connections to the supramarginal gyrus (Brodmann area 40) area were seen bilaterally and again this was greater on the left. Fig. 3C shows a plot of left and right hemisphere connecting volumes and lateralization index as a function of commonality value C . The left had a larger connected volume at all values of C , and this lateralization was greater in regions of high commonality.

Fig. 4 shows the group variability maps for the volumes of connection obtained from the temporal lobe VOIs. Extensive and consistent connections were seen bilaterally to the superior and middle temporal gyri, extending anteriorly into the temporal lobe. More extensive connections to the superior longitudinal fasciculus were seen on the left than on the right. In addition, greater fronto-temporal connections were seen via the inferior fronto-occipital fasciculus and the uncinate fasciculus inferior to it on the left than on the right. Connections were also seen posteriorly to the occipital lobe, principally to extra-striate visual cortex (Brodmann area 19). Fig. 4C shows the plot of left and right hemisphere connecting volumes from these VOIs and the associated lateralization index. Lateralization is still to the left (apart from the highest value of C)

as shown by positive LIs, although the LIs are lower than for the frontal VOIs and become smaller at higher commonality values.

Correlations between structure and function

There was a significant correlation between the degree of lateralization of mean FA and lateralization of fMRI activation for verb generation in the frontal lobes (Pearson's correlation coefficient = 0.782; $P = 0.008$, Fig. 5A) and for reading comprehension in the temporal lobes (Pearson's correlation coefficient = 0.651; $P = 0.042$, Fig. 5B), characterized by greater structural lateralization in subjects with greater functional lateralization. No significant correlation was seen between tract volumes and functional activation.

Regression analysis

Correlations between the mean FA of the left frontal connections and voxelwise fMRI activity for verbal fluency were most significant in the left supramarginal gyrus (Fig. 6A). For reading comprehension, activation within a region in the left frontal gyrus was significantly correlated with mean FA of the left temporal connections (Fig. 6B).

Discussion

We used MR tractography to demonstrate the structural connections of the cortical regions activated by expressive and receptive language tasks. A direct connection, corresponding to the SLF, was traced bilaterally between the inferior frontal and

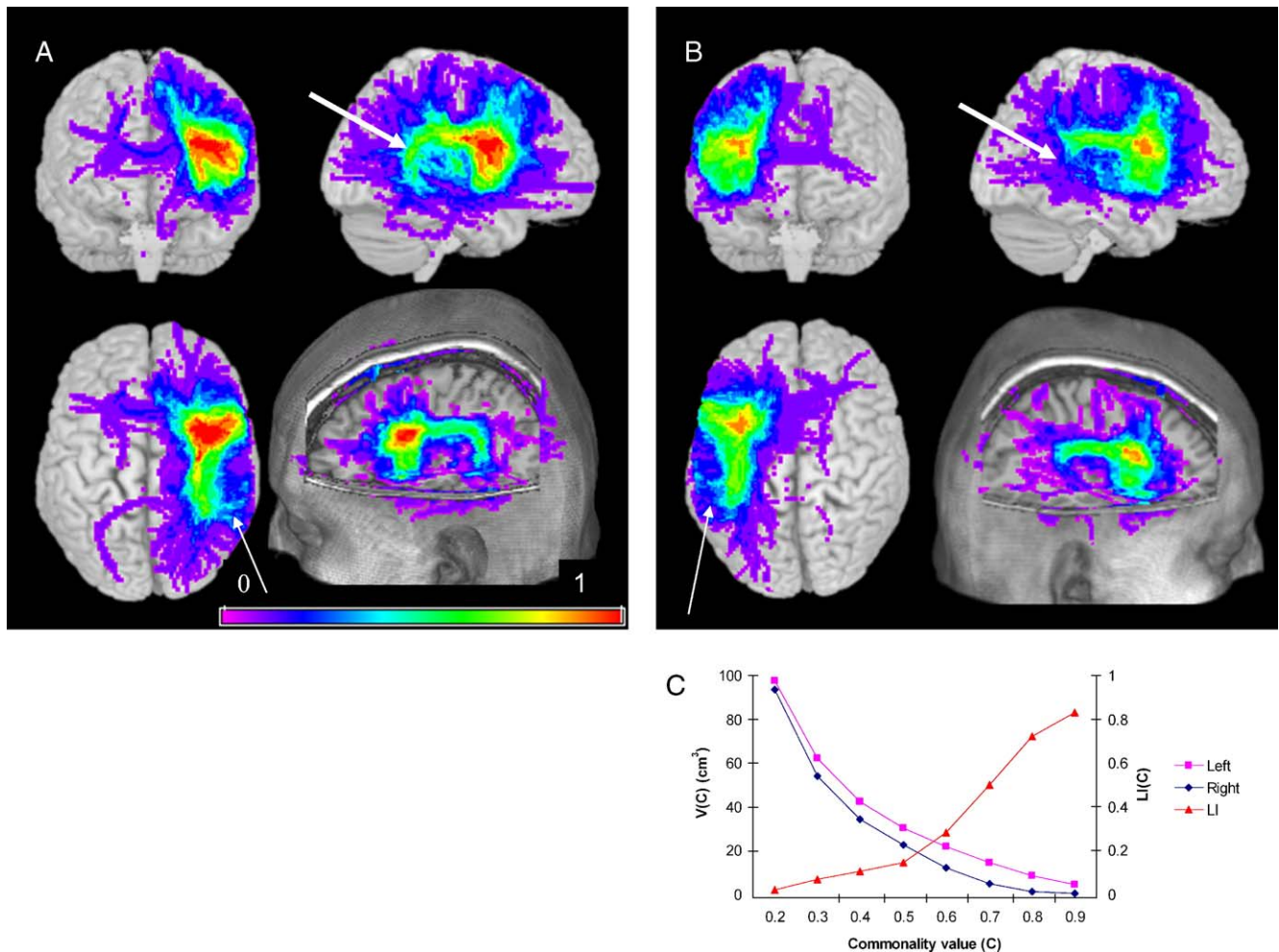


Fig. 3. Group variability maps of the connecting paths tracked from the left (A) and right (B) frontal VOIs. The first three images in each show brain surface rendering with embedded spatial distribution of connections in the coronal, sagittal and axial planes. The fourth images show homotopic sagittal slices. The color scale indicates the degree of overlap among subjects (expressed as commonality value (C)). Connections to the temporal lobe are greater on the left than the right (thick arrows) as were connections to the supramarginal gyrus (thin arrows). Panel C shows connecting volume $V(C)$ and lateralization index $LI(C)$ as a function of commonality value C . The left has a larger connected volume at all values of C and the lateralization is greater in regions of high commonality.

posterior temporal lobes, but visual inspection showed that there was a clear structural asymmetry with greater connectivity in the left hemisphere than the right. This asymmetry was most striking in the pattern of connectivity from the inferior frontal VOIs with more extensive connections to the temporal lobe on the left. Similarly, when tracking was initiated in the temporal lobes, greater connectivity to frontal regions was seen on the left. This structural asymmetry, namely greater fronto-temporal connectivity on the left, may reflect the left-sided lateralization of language function in the human brain.

We also demonstrated a significant correlation between the structural lateralization of the identified pathways and the left–right difference in functional activation in both frontal and temporal lobes, with subjects with more highly lateralized language function having a more lateralized pattern of connections. This suggests a possible relationship between brain structure and function and is, to our knowledge, the first such demonstration in the human language system.

Tracking the connectivity of white matter regions adjacent to Broca's and Wernicke's areas, and their right hemisphere homologues, also revealed connections not considered specifically

related to language function. In addition to the asymmetry seen in the language-specific pathways, stronger fronto-temporal connections via the inferior fronto-occipital and uncinate fasciculi were seen on the left. Experimental studies in monkeys have shown a monosynaptic route of connection between frontal and temporal lobes via the uncinate fasciculus (Kier et al., 2004); therefore, this increased connectivity may also reflect the greater functional role played by the left inferior frontal lobe. Connections were also seen to the supramarginal gyrus, again being more prominent on the left.

More symmetrical connections were seen extending from the temporal lobe VOIs to the anterior temporal lobe and posteriorly to the occipital lobe. Studies have suggested that the superior temporal sulcus is a multisensory area important for integrating auditory and visual information (Beauchamp et al., 2004a,b; van Atteveldt et al., 2004), and electrophysiological studies have shown individual neurons in monkey STS that respond to both auditory and to visual stimuli (Hikosaka et al., 1988). It is therefore interesting that seed points in this region demonstrate extensive connections to visual and auditory cortex, along with other connections to frontal and parietal language areas. These connections may represent a structural

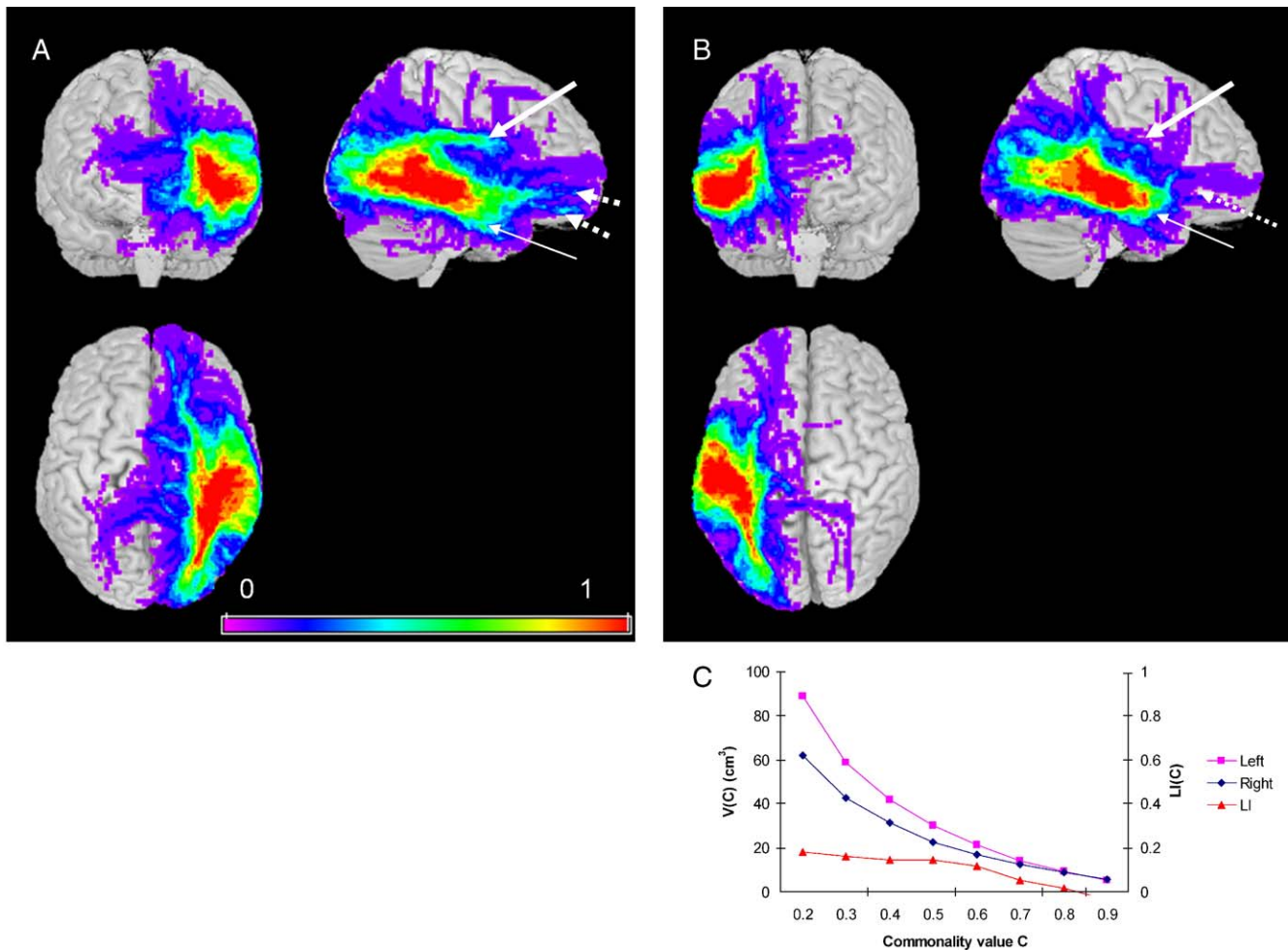


Fig. 4. Group variability maps of the connections from the left (A) and right (B) superior temporal VOIs. The color scale indicates the degree of overlap among subjects (expressed as commonality value C). Consistent bilateral connections were seen to the superior and middle temporal gyri, extending anteriorly into the temporal lobe (thin arrows). Greater fronto-temporal connections were seen on the left than on the right, both via the superior longitudinal fasciculus (thick arrows) and via the inferior fronto-occipital and uncinate fasciculi (dotted arrows). Posterior connections to the extra-striate visual cortex were relatively symmetrical. Panel C shows connecting volume $V(C)$ and lateralization index $LI(C)$ as a function of commonality value C .

framework for multimodal convergence of sensory information at a multisensory region.

A feature of human language processing is the ability of written and spoken words to access the same semantic meaning. The connections demonstrated here provide an anatomical substrate upon which this may occur and correspond to the ventral processing streams (Parker et al., 2005) from primary sensory areas converging in anterior temporal and inferior frontal regions, as described by Marinkovic et al. (2003).

We also found quantitative differences between left and right hemispheres, with the overall tract volumes being significantly higher on the left than the right. Examination of tract volumes as a function of commonality showed that the degree of left lateralization was higher for the tracts derived from the frontal lobe VOIs than for the tracts derived from the temporal lobe VOIs, and that this was higher in areas of higher commonality. Further, the mean FA of the estimated tracts derived from the frontal VOIs was also significantly higher on the left than the right. These results corresponded to the pattern of functional activation which was highly lateralized in the frontal lobes but more bilateral in the temporal lobes.

As the PICO probability threshold is increased, the volume of the connections decreases and the mean FA increases. This occurs as the core pathways are increasingly identified. Low voxel anisotropy implies higher uncertainty in fiber orientation within that voxel therefore probabilistic tracking through such regions may become dispersed, implying a larger apparent connected volume. Importantly however at any chosen probability threshold the tract volume will be lower for the tract with lower anisotropy, explaining the differences seen between left and right hemispheres, with both volumes and mean FA being greater on the left.

Defining starting regions

One other recent study has used tractography to investigate the lateralization of language pathways, also demonstrating stronger connections in the left hemisphere (Parker et al., 2005). They used anatomical guidelines to define Broca's and Wernicke's areas as VOIs for initiating fiber tracking and constrained their analysis to only identify pathways passing through both regions. The VOIs used were significantly larger in size in the left hemisphere due to the known hemispheric

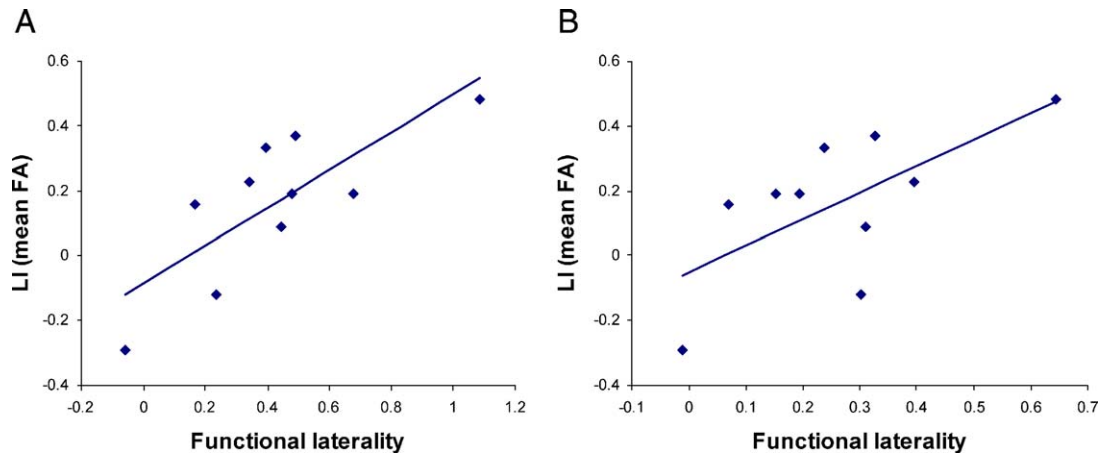


Fig. 5. Significant correlations between mean FA lateralization index ($LI = FA_{\text{left}} - FA_{\text{right}} / FA_{\text{left}} + FA_{\text{right}}$) of the pathways identified and functional laterality of fMRI activation in the frontal lobes for verb generation (A) and in the temporal lobe for reading comprehension (B).

anatomical differences in the frontal and temporal lobes (Amunts et al., 1999; Good et al., 2001; Pujol et al., 2002; Shapleske et al., 1999; Toga and Thompson, 2003). This asymmetry could possibly affect the volumes and extent of the connections obtained, although there was no correlation between the VOI volumes and the resulting volumes of connecting tracts.

Our approach provides a number of benefits over the two-VOI method for identifying regions involved in language function. Firstly, the observer bias inherent in manual VOI definition is reduced by using fMRI-derived tracking start VOIs. Secondly, by using mirror image VOIs of identical volume in the non-dominant hemisphere, the possibility of VOI-induced tract volume errors is reduced, although it could be argued that erroneous placement of the mirror image VOIs (for example, in an inappropriate gyrus) could lead to incomplete tract localization. Thirdly, the use of probabilistic tracking from single VOIs for each functional localization in each individual allows the possibility of identification of patterns of connectivity without imposing strong prior user knowledge. Lastly, the use of specific functional paradigms allows the identification of pathways associated with cortical regions involved in mediating specific tasks, rather than those associated with classically identified language-related regions.

In order to minimize operator bias in seed point selection and to ensure consistency in our method, we used the group activation peak, rather than each individual subject's own activation peak. We realize that this may reduce our sensitivity in identifying subtle differences in connection patterns between individuals but concluded that it was the most robust and reliable method for detecting group level differences between the left and right hemispheres. Performing the same study using each individual's peak activation to select start regions would be an interesting complementary study to the results reported here.

By using functionally defined VOIs, we aimed to make our method as operator-independent as possible; however, the use of fMRI to define starting points for tractography is not without problems, in particular with regard to the precise coregistration of fMRI and DTI. The steps of normalization to standard space (to obtain the group activation maps) and subsequent reverse normalization to native space, along with the differences in susceptibility and other artefacts between fMRI and DTI images are potential sources of error when coregistering the two

modalities. By defining relatively large VOIs (each consisted of 125 voxels), we tried to limit the effect of small registration errors. Spatial smoothing of the fMRI scans (performed to improve signal-to-noise and better meet the assumptions of Gaussian field theory) leads to blurring of activations across neighbouring voxels, leading to activations which include both grey and white matter. While this may initially appear problematic, one consequence is that it provided a relatively unbiased choice of white matter voxels for tractography seeding, avoiding both the complexity of trying to track deep within grey matter (where most tractography algorithms fail) and the necessity to manually define the white matter voxels expected to subservise a particular grey matter area.

The lateralization of language function inevitably leads to problems in the identification of the right hemisphere homologues to Broca's and Wernicke's areas. Our solution was to manually define right hemisphere VOIs of identical size in areas homotopic to the functionally defined regions. The aim again was to minimize operator bias, although we recognize the limitations of this approach given that structurally homotopic regions do not necessarily correspond functionally. One recent study has indeed demonstrated that right frontal activation on tasks of verbal fluency was not homologous to that seen in the left frontal lobe and that in a group of patients with left temporal lobe epilepsy the right frontal activation shifted in location (Voets et al., 2006). For the superior temporal gyrus, however, we had areas of fMRI activation from the reading comprehension paradigm in both left and right hemispheres which we used for defining left and right sided ROIs. Tracking from these regions was therefore free from operator bias, and using these bilateral functionally defined regions, we still demonstrated a left–right asymmetry in the fronto-temporal connections seen. We therefore feel that this strengthens our findings for the frontal lobe connections.

Another difference between our method and that described in the previous study (Parker et al., 2005) was the use of a single starting region and a more sensitive probabilistic tractography technique. Using a single VOI for each tracking experiment imposed fewer a priori constraints on the results. It may be the case that some pathways which play a role in certain aspects of language processing do not directly connect Broca's and Wernicke's areas (for example, the connections between Wernicke's area and visual and auditory cortex) and therefore would not be seen when the results are constrained by using

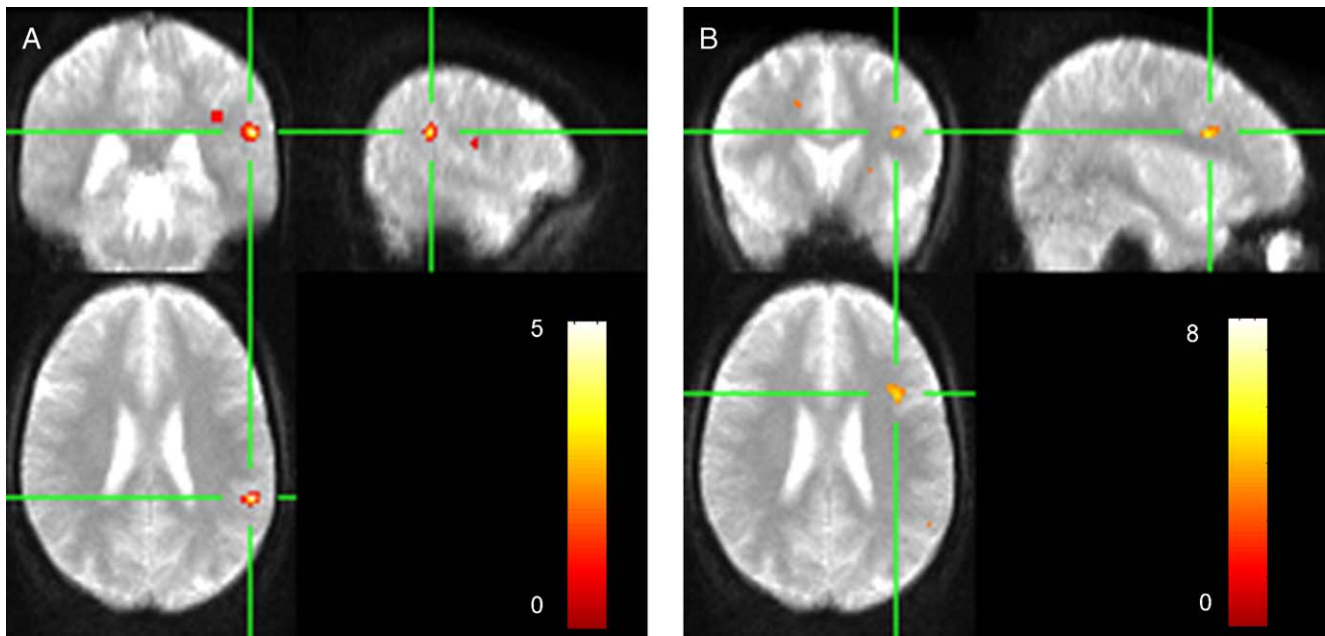


Fig. 6. Regression analysis between fMRI contrasts for (A) verbal fluency and (B) reading comprehension and the mean FA of the left frontal VOI connections. For verbal fluency, a significant correlation was seen in the left supramarginal gyrus and for reading in the left inferior frontal gyrus.

two VOIs. The two-region approach reduced the likelihood of false positive pathways but had the disadvantage of potential bias due to the a priori assumption that connections between the two sites do actually exist. As a result, clear prominence is given to apparent connections between these sites, thus ignoring other potentially interesting connections. The probabilistic algorithm adapts the commonly used streamline approach to exploit the uncertainty in one or more fiber orientations defined for each voxel. The use of a probabilistic method provides a measure of confidence, in terms of the model of diffusion employed, to the connections seen. The use of the multi-tensor model allows tracking through regions exhibiting fiber crossings such as those affecting the superior longitudinal fasciculus (Parker and Alexander, 2003). To the best of our knowledge, this is the first application of probabilistic fiber tracking using crossing fiber information.

Despite numerous differences in the methods used for establishing start points for tractography and those used for fiber tracking, our results are broadly similar to those of Parker et al. who also demonstrated larger volume of connections, particularly to the temporal lobe, on the left than the right (Parker et al., 2005). This reinforces the conclusion that this does represent a genuine biological difference between left and right hemispheres. In addition, we investigated anatomical connectivity to language-related regions defined in the superior temporal gyrus and observed a lesser degree of lateralization (Fig. 4). This suggests that the lateralization observed in the connections of Broca's and Wernicke's areas is not just an artefact of general left-sided tract dominance (Good et al., 2001).

Functional networks of language regions

Catani et al. used tractography to study perisylvian language networks in the left hemisphere (Catani et al., 2005). In addition to the direct pathway connecting Broca's and Wernicke's areas, they used a two-VOI approach to demonstrate a second, indirect

pathway passing through the inferior parietal cortex. This ran laterally to the direct pathway and was composed of an anterior segment connecting Broca's area with the inferior parietal lobe and a posterior segment connecting the inferior parietal lobe to Wernicke's area, and the authors argued that the existence of this second pathway helped to explain the diverse clinical spectrum of aphasic disconnection syndromes. This was an area that had also been shown to have connections to both Broca's and Wernicke's areas by Parker et al. (2005). Our findings are in keeping with these as we demonstrate a connection to the supramarginal gyrus (Brodmann area 40) in the inferior parietal lobe, a region implicated in a number of language-related tasks (Hickok and Poeppel, 2000; Wise et al., 2001). The single VOI approach does not allow us to distinguish whether this is a separate and discrete pathway from the other fronto-temporal connections demonstrated.

Electrophysiological evidence also supports our current findings. In patients undergoing invasive monitoring with subdural electrodes for epilepsy surgery, stimulation of the anterior language area elicited 'cortico-cortical evoked potentials' (CCEPs) in the middle and posterior parts of the superior and middle temporal gyri as well as the supramarginal gyrus (Matsumoto et al., 2004). Stimulation of the posterior temporal area produced CCEPs in the anterior language area, suggesting a bidirectional connection between Broca's and Wernicke's areas. The pattern of connections revealed in this study provides an anatomical substrate for this functional connectivity.

Structure–function relationships

We demonstrated a significant correlation between the lateralization of mean FA of the identified pathways and the left–right difference in functional activation. This correlation was seen for both frontal lobe activation during verb generation and for temporal lobe activation during reading comprehension. This suggests a difference in pathways between subjects that reflects

their degree of functional asymmetry and demonstrates an interesting relationship between structure and function.

A previous study has combined functional MRI and DTI with tractography to study structure–function relationships in the visual system (Toosy et al., 2004). It used photic stimulation to induce visual cortex activity and PICO to track the optic radiations from a seed point near the lateral geniculate body of the thalamus. The mean FA of the optic radiations correlated significantly with fMRI parameter estimates (a measure of functional activity), although, as in our study, no correlation was demonstrated for tract volumes.

In our study, the regression analysis identified regions where the mean FA of the tracts correlated with voxelwise fMRI activity. The correlation in the left frontal lobe was demonstrated during the reading paradigm and that in the supra-marginal gyrus during the verbal fluency paradigm. These were distant to the main areas of activation although still in language related regions, supporting the existence of widespread networks involved in language function.

Summary

In summary, we have combined functional MRI language tasks and probabilistic tractography to study the pattern of language related pathways in right-handed healthy control subjects. We demonstrated an asymmetry in the pattern of connectivity with greater connections between frontal and temporal lobes on the left, reflecting the lateralization of language function. The findings described here are from a group of strongly right-handed subjects, and it will be important to compare these results with those from left-handed subjects including some with atypical language dominance. Further developments including improved methods of coregistering fMRI and DTI images and quantification of tractography output will improve the delineation of language related pathways, and comparison with studies of functional connectivity will enable a better understanding of language networks and the effect of diseases upon them.

Acknowledgments

This work was supported by the Wellcome Trust (Programme Grant No.067176, HWRP, MRS), the National Society for Epilepsy (MJK, JD) and Action Medical Research (PB).

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