An objective approach to fMRI assessment of language lateralization

D. F. Abbott[1,2], A. B. Waites[1,2], and G. D. Jackson[1,3]

[1]Brain Research Institute, Florey Neuroscience Institutes (Austin), Melbourne, Victoria, Australia, [2]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia, [3]Departments of Medicine & Radiology, The University of Melbourne, Melbourne, Victoria, Australia

Introduction: Language lateralization based on functional magnetic resonance imaging (fMRI) is often used in clinical neurological settings. Currently, interpretation of the distribution, pattern and extent of language activation can be heavily dependent on the chosen statistical threshold. The aim of the present study was to develop a threshold-independent method of assessing when individual patients have statistically atypical language lateralization. The method statistically compares the relationship between laterality index (LI) and number of active voxels between a control group and a subject of interest.

Methods (data acquisition and analysis): Normative data from 34 healthy control subjects (Age rage 7 - 70, mean±SD = 27±17 years, 20 male) were analysed. Each subject performed a standard language fMRI study. This behavioural paradigm involved four 30-second blocks of task alternating with blocks of rest (visually presented cross hair). During task blocks subjects performed covert orthographically-cued lexical retrieval (OLR) – a verbal fluency task where the subject was required to generate words beginning with each of a series of displayed letters. Functional echo-planar imaging volumes of the whole brain were acquired using a GE 3 T scanner. Analysis was performed using iBrain™ (Brain Research Institute, http://brain.org.au/software) and SPM2 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). Pre-processing included slice-timing correction, motion correction (realignment), and non-linear warping to a custom local template approximating that of the standard Montreal Neurological Institute (MNI) template. Spatially normalised image data was smoothed with an 8 mm isotropic Gaussian kernel and images were saved at a uniform voxel size of 3x3x3mm. Using the general linear model (GLM), statistical parametric maps were computed for each dataset. Temporal autocorrelation was modelled using a white noise and autoregressive AR(1) model. Motion correction parameters were included as covariates of no interest.

Methods (laterality): Laterality index (LI) within a region of interest (ROI) was calculated for each subject. The ROI was defined using a combination of functional and anatomical landmarks. The functional landmark consisted of voxels shown to be significantly involved in language function from a random effects analysis of an independent cohort of 30 healthy subjects (Waites AB et. al., 2006, Ann Neurol 59, 335-343). The region was made symmetric by mirroring all contralateral voxels. We then defined a left cortical and right cortical ROI (L and R) by choosing only lateral cortical regions in each hemisphere. Laterality index was calculated as: $LI=(N_L-N_R)/(N_L+N_R)$ where N_L and N_R number of voxels above a chosen threshold in each of the left and right ROIs respectively. **Our method** requires one to calculate for an individual the distribution of LI as a function of number of voxels above threshold ("LI-distribution"). One then determines whether the individual has atypical laterality by statistically comparing their LI-distribution to a group of LI-distributions calculated in a similar manner for a number of healthy controls. In practice we limit the comparison to a range of thresholds at which the LI values of the control group are normally distributed, as determined using the Jarque-Bera normality test, and in which at least half the control group contributes (since the maximum positive voxel count exhibited by unthresholded t-maps will not be the same for every subject). The probability (p-value) of the laterality of a subject being consistent with the control group is obtained by first subtracting from each subject's LI at each voxel-count the control-group mean LI at that voxel-count (yielding at each voxel count an adjusted control distribution with zero mean and an adjusted value for the individual). Then for each subject we average across the voxel-count range determined above – this yields one average value per subject. A one-tailed unpaired Student's t-test is then undertaken between the distribution of control-group averages and the average of the individual subject in question.

Results: Normative data is shown in figure1. This illustrates the benefit of the adaptive number-of-voxel threshold approach that permits statistical testing between the control curves and an individual as shown in two example cases in figure 2.

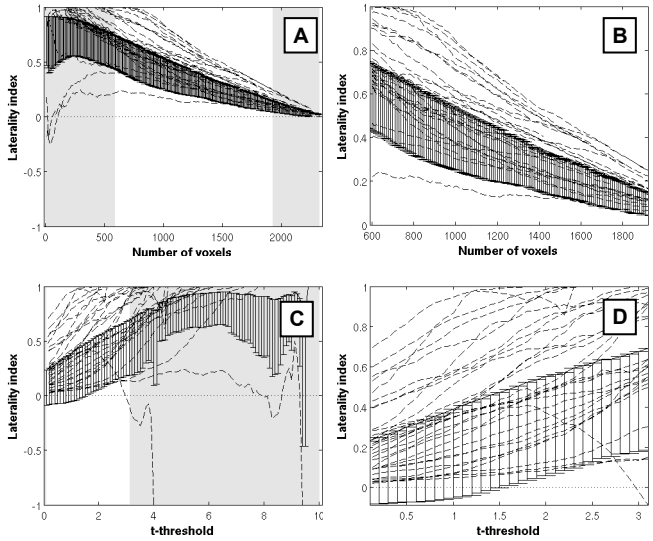

Figure 1. Plots A & B show the variability across 30 subjects of laterality index (LI) as a function of number of active voxels within language regions. Each subject is shown in a dashed line. Overlaid is the mean curve (bold line) together with the 95% CI for the one sided t-test, below which a subject is considered atypical in their language distribution. In the shaded area in A the distribution of LI's is unlikely to follow a normal distribution according to the Jarque-Bera normality test and/or fewer than half the controls have this many active voxels. Plot B shows an expanded view of the "valid" (non-shaded) area of A. Plots C and D follow a similar convention to A and B except they show LI plotted as a function of t-threshold, demonstrating the proposed method would not be suitable for LI vs t-score distributions. Notice that the 95% confidence intervals are much better (smaller and more distant from the zero bilateral line) for plot B compared to plot D.

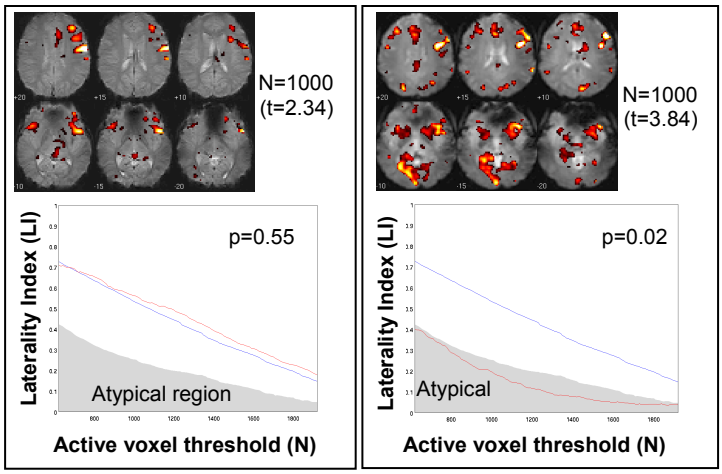

Figure 2: These panels show summary data for two subjects as one might display it in a clinical setting. The red line is the subject in question. The blue line is the mean of the control distribution. The shaded area is the region in which the subject would be considered atypical. The second subject above would be considered atypically bilateral (if the subject were right lateralised, their plot would extend down to negative values on the y axis). The choice of number of voxel threshold at which to view the image is not critical so long as the laterality curve displays a consistent laterality. If the LI curve was ambiguous (crossing between the atypical and typical region) then viewing the image at different thresholds on either side of the crossing would be advisable.

Conclusion: The proposed method provides a robust and objective indication of atypical lateralization, displaying more comprehensive information than conventional methods. The method could be used more generally to assess relative regional distribution of activity in other neuroimaging paradigms (for example, one could apply it to the assessment of lateralisation of activation in a memory task, or to the assessment of anterior-posterior distribution rather than laterality).