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Sex differences in the functional organization of the brain for language

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A MUCH debated question is whether sex differences exist in the functional organization of the brain for language[1–4]. A long-held hypothesis posits that language functions are more likely to be highly lateralized in males and to be represented in both cerebral hemispheres in females[5,6], but attempts to demonstrate this have been inconclusive[7–17]. Here we use echo-planar functional magnetic resonance imaging[18–21] to study 38 right-handed subjects (19 males and 19 females) during orthographic (letter recognition), phonological (rhyme) and semantic (semantic category) tasks. During phonological tasks, brain activation in males is lateralized to the left inferior frontal gyrus regions; in females the pattern of activation is very different, engaging more diffuse neural systems that involve both the left and right inferior frontal gyrus. Our data provide clear evidence for a sex difference in the functional organization of the brain for language and indicate that these variations exist at the level of phonological processing.

We studied neurologically normal right-handed males (mean age 28.5 years) and females (mean age 24.0 years). Subjects performed four distinct same–different tasks on visually displayed stimuli: line judgement, letter case, rhyme and semantic category. The decision (same versus different) and response components (pressing a response bulb for same pairs) of these tasks are comparable, but there is a difference in the type of linguistic information engaged by each. In the line-judgement task, subjects viewed two sets of four lines with right or left orientations, one above the other, and determined whether the upper and lower displays had the same pattern of left/right alternation (engaging visual information processing). In the letter-case judgement task, two sets of consonant strings were displayed, and subjects determined whether they contained the same pattern of case alternation (engaging both visual and orthographic processing). In the rhyme-judgement task, subjects determined whether two nonsense word strings rhymed (engaging visual, orthographic and phonological processing: subjects must map the letter strings onto phonological representations). Finally, in the semantic category task, subjects determined whether two words came from the same semantic category (engaging visual, orthographic, phonological and semantic information). By subtracting the line from the case task, activation in regions of interest associated with orthography can be isolated; by subtracting the case from the rhyme task, phonological regions of interest can be isolated; and by subtracting the nonsense word rhyme from the semantic category task, regions of interest associated with lexical semantic processing can be isolated.

Selection of candidate regions of interest was motivated by previous neuropsychological and neuroimaging investigations of language function. Behavioural research on word recognition isolates two types of coding relevant to lexical identification: orthographic (pertaining to letter encoding) and phonological (pertaining to phoneme encoding)[22,23]. Preliminary analysis identified one region uniquely associated with orthographic processing (extrastriate, ES). A second region, located within the superior aspect of the inferior frontal gyrus, roughly encompassing Brodmann's areas 44/45 (which we term IFG) and previously shown to be activated in speech tasks when phonetic decisions are required[24,25], was found to be uniquely associated with phonological processing on rhyme judgements. The rhyme-judgement task was also associated with activation at sites in both the superior temporal gyrus and middle temporal gyrus, areas that fall within traditional language regions. But the semantic task activated both of these areas significantly more strongly than the rhyme task, suggesting that these regions subserved both phonological and lexical semantic processing. The IFG, by contrast, was uniquely associated with phonological processing, and here we focus on the contrast between IFG and ES regions in examining sex differences.

A $2 \times 2 \times 3 \times 3$ analysis of variance (ANOVA) was performed with the following factors: region of interest (IFG versus ES), hemisphere (left versus right), task (case versus rhyme versus semantic), and sex (male versus female). For each subject, the number of pixels showing significant changes in magnetic resonance signal intensity was computed in the initial split *t*-test (Fig. 2) and these values were subsequently entered as the dependent measure in the ANOVA.

A significant sex-by-hemisphere interaction was observed: $F(1, 36) = 14.74$, $P < 0.001$. For males, the mean number of pixels activated were 11.7 and 5.0 for the left and right hemispheres, respectively; the corresponding values for females were 9.4 and 12. As shown in Fig. 1, activation during rhyming in males was lateralized to the left inferior frontal regions. In contrast, activation during this same task in females engaged this region

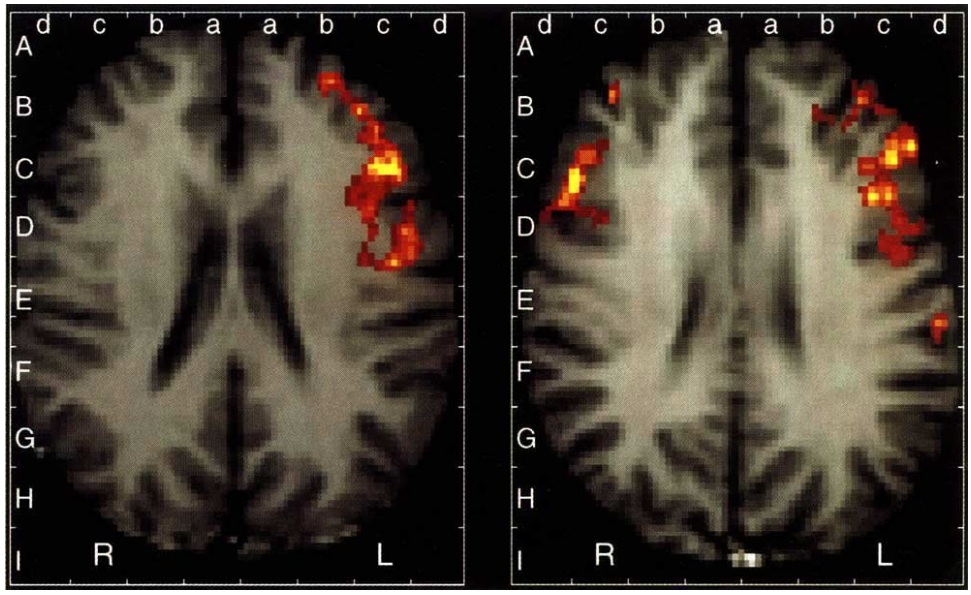

FIG. 1 Composite images of the distribution of activations comparing rhyme-case tasks (phonological processing) for 19 males (left image) compared to 19 females (right image). Colour dots represent pixels for which the mean value of the split *t*-statistic from averaging the 19 subjects was higher than 0.4 (dark red dots are close to 0.4; yellow approaches 1.0). The images were cluster-filtered so that isolated activated pixels without at least four activated neighbours were dropped. Images were coregistered using a piece-wise warping algorithm. Six image subregions were identified as described in Fig. 2 legend and each was linearly scaled so that the anatomic reference points (the anterior and posterior commissures and midline) and brain edges aligned. Coordinates[29] were then assigned to each region. Activations are shown for level 6–7 ($z=20$) of the Talairach system[29]. The Talairach reference grid has been superimposed on each image. Capital letters A–I (*y*-axis) and lower-case a–d (*x*-axis) designate the Talairach proportional grid system. R and L are right and left sides of brain, respectively. Sections are oriented with anterior portions at top of figure. Males show unilateral activation, primarily in the left inferior frontal gyrus (centred on coordinates $x=5.0$, $y=1.8$, $z=20$), with minor activation of the left middle frontal gyrus. In females, phonological processing activates both the left (L) and right (R) inferior frontal gyri. There is smaller activation of the left and right middle frontal gyri (centred on coordinates $x=3.4$, $y=4.5$, $z=20$) and of the left post-central gyrus (centred on coordinate $x=6.0$, $y=-2.1$, $z=20$).

METHODS. Imaging was performed on a 1.5 Tesla GE 'Signa' MR imaging system equipped with echo-planar imaging (EPI) hardware from Advanced NMR (Wilmington). Conventional spin echo sagittal T_1-weighted (TE (echo time), 11 ms; TR (repetition time), 500 ms; FOV (fieldof view), 24 cm; slice thickness, 5 mm; slice gap, 2.5 mm; 256 × 128 × 1Nex (number of excitations)) localizer scans were first obtained from which axial–oblique activation images were prescribed. Three axial–oblique slices, 8 mm thick, were obtained parallel to a line connecting the anterior and posterior commissures. The inferior slice was centred at Talairach 9, the middle slice at Talairach 7–8, and the superior slice at Talairach 6–7. Conventional spin echo images (TE, 11 ms; TR, 500 ms; FOV, 40 × 40 cm; 256 × 192 × 2 Nex) of these slice locations were collected before the start of each activation paradigm. These anatomic images, which are in exact registration with the activation images, were later used as the basis images on which to overlay activation maps. Subjects' heads were immobilized within the head coil by using a neck support, foam wedges and a restraining band drawn tightly around the forehead. The calculated *t*-maps showed no significant rim artefacts or apparent activation at strong edges, confirming that head movements were not significant.

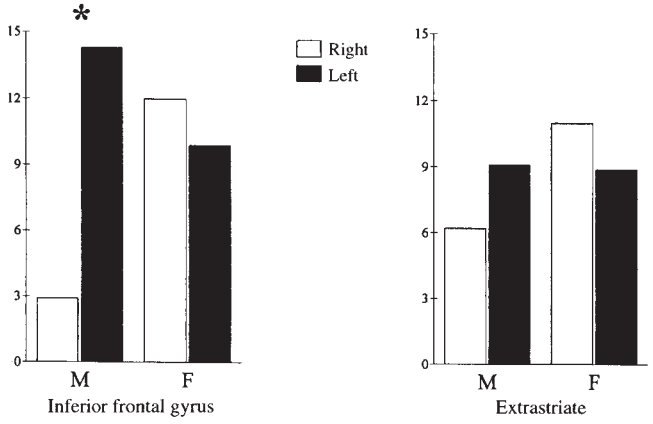

FIG. 2 Three-way interaction between region of interest, hemisphere and sex. Ordinate represents mean activations across tasks for inferior frontal gyrus and extrastriate regions, respectively. Overall $F(1, 36)=7.77$, $P<0.01$. For females (F), the means for left (black bars) and right (grey bars) extrastriate were 8.9 and 11.0, and for left and right inferior frontal gyrus region were 12.0 and 10.0; these means were not significantly different. For males (M), the corresponding means were 9.1 and 6.2 for left and right extrastriate, and 14.3 and 2.9 for left and right inferior frontal gyrus region. The difference for males in the inferior frontal gyrus region is significant, $F(1, 18)=22.34$, $P<0.001$ (indicated by asterisk). To examine this three-way interaction further, the sex by hemisphere interaction was analysed for the two regions separately. The sex by hemisphere interaction was highly reliable in the inferior frontal gyrus region, $F(1, 36)=20.90$, $P<0.001$) but nonsignificant in extrastriate regions ($P>0.05$). We further examined the ratio of right hemisphere to left hemisphere activation in the IFG. Eleven of 19 females but no males had a right to left hemisphere ratio ≥ 0.70; in fact for 9 of these 11 females the ratio was ≥ 1.0. Thus, more than half of the female subjects produced strong bilateral activation in this region; by contrast, no males showed this pattern.

METHODS. Data analysis was performed using software written in MATLAB (Mathworks, Natick, MA). The activation images were collected using an EPI gradient echo sequence (flip angle, 60°; TE, 45 ms; TR, 1,500 ms; FOV, 40 × 20 cm; 128 × 128 × 1 Nex) in the three slice locations described. Twenty-four images per slice location were collected while the subject performed one of the four (line, case, rhyme or semantic) activation tasks. Each task was run 4 times, with the order of successive tasks randomized, a total of 96 images per slice per task being collected. The first seven images from each series were dropped because they were obtained before a steady state of the echo-planar sequence was reached The remaining seventeen images from each series were median-filtered. Before median filtering, the temporal mean intensity image was subtracted from each acquisition and added back after filtering. Subject head movements were analysed but not corrected. When movements larger than one pixel were found, those image data were discarded and only the unshifted data were analysed. There was no significant artefact from motion effects at the edges that could produce false activation in functional MRI. The activated pixels were detected for each pair of activation tasks using a split Student *t*-test. The split *t*-test divides the data into two parts and performs a separate *t*-test on each half dataset. If the *t*-value for a given pixel from both *t*-maps was above 2, the pixel was considered to be activated. This analysis does not correct for any residual temporal correlation between successive images that can arise when the activation response varies during the task[30], but these corrections to our *t*-values are negligible for the steady-state response achieved during our experiments. For normally distributed data, $t>2$ corresponds to $P<0.05$. This threshold for activation provides a consistent criterion for identifying true activity from other sources of signal variation. On each anatomical image, the positions of the anterior commissure and posterior commissure and the direction of the midline were found manually. These reference points and the edges of the brain let us define the standard Talairach coordinate system for each subject. Each brain (anatomical image and activation map) was then rescaled to the standard Talairach form using cubic proportional fitting for each block defined by the anatomical landmarks. This procedure was remarkably successful; the major sulci and gyri can be clearly recognized on the composite image obtained by adding 38 Talairach-scaled anatomical images. Finally, each anatomical region of interest was identified in the Talairach coordinate system and approximated by a set of squares (Fig. 1). The number of activated pixels in each region was then used as a measure of the level of activation for any pair of tasks.

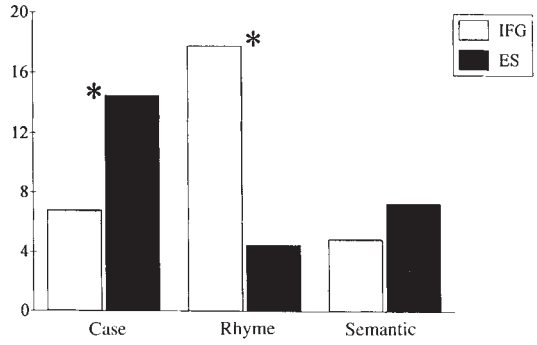

FIG. 3 Task by region of interest. Ordinate represents mean activations for case, rhyme and semantic subtractions in the inferior frontal gyrus (IFG; grey bars) and extrastriate (ES; black bars) regions, respectively. A significant interaction between task and region was observed, $F(2, 72) = 9.94$, $P < 0.001$. The means for the case, rhyme and semantic subtractions in the IFG region were 6.8, 17.8 and 4.9; corresponding means in the extrastriate region were 14.5, 4.5 and 7.3, respectively. Separate contrasts revealed that in the IFG region rhyme significantly differed from both case, $F(1, 36) = 10.0$, $P < 0.001$, and semantic, $F(1, 36) = 13.88$, $P < 0.001$, whereas case and semantic did not differ ($F < 1.0$). In the extrastriate region, case significantly differed from both rhyme $F(1, 36) = 8.37$, $P < 0.001$, and semantic, $F(1, 36) = 4.27$, $P < 0.05$. The rhyme and semantic conditions did not differ ($F < 1.0$). To test the hypothesis further that extrastriate areas subserve orthographic processing while the IFG region subserves phonological processing, we contrasted activation produced in a rhyme–case versus a rhyme–line subtraction. By the logic of the design, the former subtraction differs only in phonology whereas the latter subtraction differs in both orthography and phonology. A significant difference between these two subtraction conditions should therefore be observed in the extrastriate as only the rhyme–line should isolate orthography and there should be no difference in the IFG region as both conditions should isolate phonology. As expected, the effect was significant in the extrastriate area, $F(1, 36) = 17.89$, $P < 0.001$. The means were 4.5 and 19.0 for the rhyme–case and rhyme–line conditions, respectively. In the IFG region, the contrast was not significant ($P > 0.10$) with means of 17.6 and 23.1 for the rhyme–case and rhyme–line conditions, respectively. Asterisks indicate tasks that significantly differ between regions ($P < 0.001$).

bilaterally. Error rates on each task were extremely low (on average one error per 20 trials) and did not vary systematically with task or by sex, suggesting that the tasks did not differ significantly in their difficulty. The three-way interaction between region of interest, hemisphere and sex was significant ($F(1, 36) = 7.77$, $P < 0.01$) and is shown in Fig. 2. Activation in the IFG region was left-lateralized for males but bilateral for females, whereas extrastriate activation was bilateral for both males and females. In addition, these analyses confirmed that the case-line subtraction (which isolates orthographic processing) more strongly activates extrastriate sites whereas the rhyme-case subtraction (which isolates phonological processing) more strongly activates the IFG region (Fig. 3).

The regions of interest examined encompass those areas traditionally considered to be critical for language[26–28]. We recognize, however, that our study does not provide information about every possible brain region and that there may be other sites relevant to phonological processing which may not show gender differences. Although we do not want to claim that phonological processing makes no demand on right hemisphere sites in males, we wish to emphasize that in a site uniquely serving phonological processing, the IFG, females devote greater right hemispheric resources to the task.

Our results indicate that it is now possible to isolate specific components of language and, at the same time, to relate these language processes to distinct patterns of functional organization in brain in neurologically normal individuals. Using this strategy, we have demonstrated remarkable differences in the functional organization of a specific component of language, phonological processing, between normal males and females. Future studies designed to examine either gender differences in language function or the neural mechanisms related to language, for example, should be specific for the component of language assessed and determined in both males and females. □

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Integration of motion and stereopsis in middle temporal cortical area of macaques

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THE primate visual system incorporates a highly specialized subsystem for the analysis of motion in the visual field[1–6]. A key element of this subsystem is the middle temporal (MT) cortical area, which contains a majority of direction-selective neurons[1–3]. MT neurons are also selective for binocular disparity (depth), which is perplexing given that they are not sensitive to motion through depth[7]. What is the role of disparity in MT? Our data suggest an important link between disparity and transparent motion detection. Motion signals in different directions tend to inhibit each other within a given MT receptive field[8]. This inhibi-

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