

# Cerebral organization of component processes in reading

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## Summary

The cerebral organization of word identification processes in reading was examined using functional magnetic resonance imaging (fMRI). Changes in fMRI signal intensities were measured in 38 subjects (19 males and 19 females) during visual (line judgement), orthographic (letter case judgement), phonological (nonword rhyme judgement) and semantic (semantic category judgement) tasks. A strategy of multiple subtractions was employed in

order to validate relationships between structure and function. Orthographic processing made maximum demands on extrastriate sites, phonological processing on a number of frontal and temporal sites, and lexical–semantic processing was most strongly associated with middle and superior temporal sites. Significant sex differences in the cerebral organization of reading-related processes were also observed.

**Keywords:** fMRI; reading; phonology; orthography; semantic processing

**Abbreviations:** fMRI = functional magnetic resonance imaging; LH = left hemisphere; RH = right hemisphere; ROI = region of interest

## Introduction

Identification of the neuroanatomical systems engaged by language processes in speech and reading represent a priority for cognitive neuroscience. Opportunities to link specific component operations in cognitive processing with brain organization have been greatly expanded by recent developments in neuroimaging technology. The new tools have profound implications for understanding the working of the normal brain, as well as for extending knowledge of the clinical disorders of language. Historically, examination of persons with focal brain damage offered the only means for establishing structure/function relationships. While studies of this sort are critical in hypothesis development, the difficulties of inferring function from deficits associated with brain lesions alone are well known (Patterson and Besner, 1984).

Development of PET techniques within the last decade offered the first opportunity to isolate dedicated anatomical

systems engaged by cognitive tasks in subjects without neurological impairments (Petersen *et al.*, 1989; Wise *et al.*, 1991; Demonet *et al.*, 1992; Petersen and Fiez, 1993). More recently, the development of an alternative imaging methodology, fMRI, makes it possible to detect blood flow/oxygenation changes (associated with brain activation) in individual subjects during the performance of cognitive tasks. Preliminary studies have demonstrated that fMRI can provide information about both the location and the magnitude of responses to stimuli of various types (Constable *et al.*, 1993; McCarthy *et al.*, 1993). [As first demonstrated *in vivo* by Ogawa *et al.* (1990, 1992) the oxygenation state of haemoglobin influences the transverse magnetization decay time of brain tissue water, a property which offers the potential for detecting the effects of altered blood flow and oxygen balance in tissues. As the concentration of deoxyhaemoglobin decreases, the intensity of the tissue

MR signal increases because deoxyhaemoglobin acts as an endogenous susceptibility contrast agent that shortens the decay time (*see also Constable et al., 1993; Schad et al., 1993*.) In a previous study conducted in our laboratory we demonstrated the utility of this approach in isolating cortical sites associated with language functions (Shaywitz *et al., 1995a*). The present study represents an extension of this previous work using fMRI procedures and tasks specifically designed to isolate component processes in reading. This study, which was driven in part by a consideration of theoretical issues raised by behavioural studies of reading, sought to isolate cortical networks associated with orthographic, phonological and lexical-semantic processes in reading words.

Most psychological theories of word identification in reading suppose that at least three distinct computational systems are engaged by a printed word: orthographic (including those processes which result in letter identification), phonological (including those processes which result in the identification of the phonemic constituents of the printed message) and lexical-semantic (including those processes which result in the successful identification of the word's meanings, rendering that information available for all higher level processing). Debate centres on the specific ways that these processes interact to produce successful word identification (Carr and Pollatsek, 1985; Seidenberg and McClelland, 1989; Van Orden *et al., 1990; Lukatela and Turvey, 1991, 1993, 1994; Pugh et al., 1994*). For instance, an assumption contained in 'dual-route' models of reading [*see Coltheart et al. (1993) for a discussion of these models*] is that access to a word's meaning can be accomplished via a direct orthographic to lexical route or through a phonologically mediated route. The direct route consists of mappings from the word's orthographic form to its lexical-semantic representation. The mediated route, by contrast, is thought to involve initial processes that map letters or letter clusters onto phonological structures (called assembled phonology) and beyond this, processes that map these phonological representations onto the lexical-semantic system.

A dominant view for many years was that with increased reading experience the direct route will carry lexical access to a greater extent than the phonologically mediated route (Coltheart *et al., 1993*). However, more recent investigations using a variety of experimental tasks suggest a prominent role for assembled phonology in word identification even for skilled readers coping with high frequency words (Van Orden *et al., 1990; Lukatela and Turvey, 1991; 1993, 1994; Perfetti and Bell, 1991; Van Orden and Goldinger, 1994*). We believe that the debate about the processing dynamics of language systems can be informed by establishing links to the functional organization of brain. If, however, we are to exploit neuroimaging techniques successfully to test hypotheses about the ways in which orthographic, phonological and lexical-semantic systems interact in reading performance, a necessary first step is to identify the cortical regions most strongly

associated with each type of processing, and this is a primary aim of the present study.

Like many previous neuroimaging studies, the present work makes use of a subtraction methodology in attempting to isolate brain/cognitive function relationships (Sergent, 1992; Friston *et al., 1993; Petersen and Fiez, 1993*). The logic of this approach is as follows. Patterns of metabolic activity are monitored while subjects perform a cognitive task which involves a given process X, among others. A control task is designed which, in principle, shares all cognitive operations with the experimental task except X. By subtracting the activation produced in the control task from the activation produced in the experimental task, regions associated with process X can, in theory, be isolated. However, it has been noted many times that some of the assumptions inherent in this approach are tenuous at best (McClelland, 1979; Sergent, 1992). Accordingly, the current study attempts to evaluate these assumptions systematically using multiple subtractions.

One assumption inherent in the subtraction approach is that adding or deleting a given cognitive operation when changing the task leaves the other operations unchanged. A good deal of research in cognitive psychology has demonstrated that information processing systems, even those probably consisting of temporally ordered stages of processing, are not simply serial and unidirectional (McClelland, 1979). Changing the conditions of a task may not result simply in adding or deleting a stage; it may also change the way that stages common to both conditions are functioning. This notion of forward and backward communication suggests highly interactive systems, a view central in connectionist models of cognitive function (Van Orden *et al., 1990*). The implication is that when using subtraction approaches to isolate a given function, changes in activation obtained may not only reflect the operation of the target process alone; they may also reflect changes in shared processes.

Another difficulty with this approach is the lack of control over how subjects actually perform tasks. While we may assume that two tasks differ on only a single cognitive dimension, the experimental demands on subjects might well encourage task specific strategies unrelated to the critical function so interpretation of activation patterns may be problematic. Thus, a given control task which in principle differs from the experimental task on a single dimension only may actually differ on any number of uncontrolled dimensions due to task induced strategies (Sergent *et al., 1992*). The importance of choosing an appropriate control task is supreme, and yet establishing just what is appropriate is certainly not easy.

Our approach to dealing with the many potential difficulties associated with subtraction approaches is to (i) employ a carefully constructed set of tasks which tap component processes in reading differently, but which share as many secondary operations as possible, and (ii) use a variety of subtractions in order to determine the function of a given

cortical region with different control and/or experimental tasks. Thus, we have built into the current experiment a consistent means of checking validity/reliability; conclusions about the function of a given cortical region will be contingent on consistency across subtractions. The details of our approach are described below.

Another potentially important issue examined in the present experiment concerns the possibility of sex differences in the functional organization of the brain for reading and language. A number of behavioural studies using paradigms such as dichotic listening or visual field manipulations have suggested that males may be, on average, more left lateralized for language than females (McClone, 1980; Lukatela *et al.*, 1986; Crossman and Polich, 1988; Zaidel *et al.*, 1995). The present study, by examining component processes in reading and by measuring cortical activation patterns in the left and right hemispheres (LH and RH) provides an opportunity to acquire more direct evidence for sex-related laterality differences.

In addition to the evidence from studies of laterality effects in normal subjects, it has also been argued from lesion studies that females have more focal language organization within the LH (Kimura, 1987). The hypothesis of more restricted language related sites in females will also be investigated in the present study. With fMRI techniques we can specifically examine the spatial extent of activation in a given region of interest (ROI).

### *Task design and processes isolated*

A hierarchical subtraction paradigm was employed in order to isolate brain regions associated with orthographic, phonological and lexical-semantic processing. While we do not assume that these processes necessarily operate in strict serial and unidirectional fashion in reading (as noted above the precise way in which these processes are engaged and interact with one another is hotly debated) it is nevertheless the case that they are logically ordered. So, for instance, assembling a phonological representation hinges on orthographic identification and accessing lexical-semantic information depends on some mix of both orthographic and phonological coding (Van Orden *et al.*, 1990; Coltheart *et al.*, 1993; Pugh *et al.*, 1994).

Subjects performed four distinct tasks; the decision (same versus different pairs) and response components (pressing a response bulb for matched pairs) of these tasks are comparable across tasks, although in each task the type of linguistic information required to make the judgement differs. In a 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 (*see* Table 1). This task should primarily engage visual-spatial feature processing. In a letter case judgement task (upper and lower case), two sets of consonant strings were displayed and subjects determined whether they contained the same pattern of case alternation. This task engages, at minimum, both visual-spatial and

orthographic (letter) processing. In a rhyme judgement task, subjects determined whether two nonsense word strings rhymed. This task engages visual-spatial, orthographic and assembled phonological processing (assembled phonology refers to those operations which map letter strings into appropriate phonological representations). Finally, in a semantic category task, subjects determined whether two words came from the same semantic category. This task engages, visual-spatial, orthographic, phonological and semantic information.

### *One-step subtractions*

Our assumptions concerning subtractions are as follows. By using the line task as a subtraction control for the case task, activation in regions associated with orthographic processing can be isolated, since the two tasks both engage visual-spatial processing but only the case task engages letter processing (*see* Table 1). Similarly, by subtracting the case task from the rhyme task regions associated with assembled phonological processing (i.e. revealing the increase in activity when progressing from orthography to phonology) can be isolated, since the tasks differ primarily on that dimension. Finally, by subtracting the rhyme task from the semantic category task, regions associated with lexical-semantic processing can be isolated, since only the latter task engages this type of processing (i.e. by using nonsense word stimuli in the rhyme task spurious activation of semantic sites should be averted).

### *Common baseline subtractions*

The present experimental paradigm also allows us to test additional hypotheses concerning the relative demands made by each task on a given region by comparing the activation produced by each with respect to another condition—a 'common baseline' condition. This is accomplished by using the line-judgement task as a baseline for the case, rhyme and semantic category tasks. This particular subtraction is important due to the possibility that certain positive differences in signal intensity (significant activations) in the three one-step subtractions could arise in a given region if the control task deactivates the region while the experimental task actually does little. With three different control tasks in the one-step analysis this possible artifact is notable. However, by examining each task relative to a common baseline we can compare them somewhat more directly within each region. Critically, if the one-step and common baseline subtractions produce comparable results regarding structure/function relationships in different regions our confidence that the results are not artifactual will be increased. Finally, the common baseline subtractions allow us to test the assumption that each subsequent task is actually adding specific cognitive operations not engaged by previous ones. On that assumption, it follows that the number of cortical sites activated should increase progressively from the case-line to the rhyme-line to the semantic category-line subtraction conditions.

**Table 1** Tasks and subtractions with processes engaged and isolated

Task/subtraction	Stimuli (matched pairs)	Processes engaged	Processes isolated
<b>Task</b>			
Line	//\ - //\	Visual-spatial	
Case	BtBT-BtBT	Visual-spatial+orthographic	
Rhyme	LETE-JEAT	Visual-spatial+orthographic	+phonological
Category	CORN-RICE	Visual-spatial+orthographic +phonological+semantic	
<b>Subtraction</b>			
Case-line			Orthographic
Rhyme-line			Orthographic+phonological
Rhyme-case			Phonological
Category-line			Orthographic+phonological+semantic
Category-rhyme			Semantic
Category-case			Phonological+semantic

### Converging subtractions

By examining additional subtractions where relevant, converging evidence regarding structure/function relationships can also be obtained. For example, if in the one-step subtractions a given region shows stronger activation in the case-line subtraction compared to the rhyme-case or semantic category-rhyme subtraction conditions we would assume that this region is primarily associated with orthographic processing. If this is so, then by extension, a comparison of the rhyme-line (two-step) and rhyme-case (one-step) subtractions should show greater activation in the former condition. This is expected since only in the rhyme-line subtraction, but not the rhyme-case subtraction, do the tasks differ on an orthographic dimension (*see* Table 1). Similarly semantic category-line should activate the region since the tasks differ on the orthographic dimension while semantic category-case or semantic category-rhyme should not, because for both of these subtractions the tasks do not differ on an orthographic dimension. Hence, a pattern including significant effects in some subtractions and non-significant effects in others is required to satisfy the convergence requirement. Accordingly, for each region analysed all potentially informative subtractions will be employed to validate the conclusions drawn from the common baseline and one-step analyses.

In summary, by using a set of tasks which differ critically in the language processes necessary to perform them combined with multiple subtractions, we can test the hypothesis that given regions serve particular functional roles in reading. If a consistent pattern of findings is observed across multiple and converging subtractions (using different experimental and/or control tasks but logically isolating the same function) our confidence in the validity of the conclusions will be greatly enhanced.

### Method

#### Subjects

Thirty-eight right handed neurologically normal subjects participated in the study. There were 19 female (mean age 24.0 years) and 19 males (mean age 28.5 years). All had received some post-graduate training in a variety of fields. None of the subjects had any history of learning disabilities.

#### Materials and procedure

The line-judgement task used visually presented displays of two sets of four lines each, presented one above the other (*see* Table 1). Each line had either a right or left orientation and subjects judged whether the top and bottom displays had the same pattern [e.g. //\/(top) and //\/(bottom) would constitute a matched pair]. Subjects responded to matched pairs by pressing a response bulb. Half of the sets were matched and half different. The case judgement task used two consonant displays, one printed above the other, with varying letter case [e.g. B t b T (top) B t b T (bottom)]. Again, half of the displays were matched and half different. If the upper and lower displays had the same pattern of upper- and lower-case alternation subjects responded positively; if they differed, no response was made. In the rhyme judgement task two pronounceable nonsense 'nonword' letter strings were displayed, one above the other. If the two strings rhymed the subjects responded positively. Care was taken to choose a large number of pairs in which the targets rhymed but the spelling was quite dissimilar (e.g. GOOZ-REWS) in order to disallow orthographic based responding. Half of the pairs rhymed and half did not. In the semantic category task real word pairs were used. Subjects responded positively if both words were from the same semantic category (e.g. CORN-RICE). Half of these pairs

were matched by category and half were not. Four sub-lists of 20 stimulus-pairs were created, for each task to form a set of 80 pairs for each task. The 16 lists (four for each task) were presented in a fixed alternating sequence. Stimulus pairs were presented at a rate of once every 4 s. Subjects responded to matched pairs (positive trials) by pressing a response bulb. The total session took ~90 min. Error rates on all four tasks were quite low (on average, ~1 in 20 trials) and did not vary systematically among tasks. Latency data could not be recorded in this study.

### Image processing

Imaging was performed on a 1.5 Tesla G.E. 'Signa' MRI system equipped with echo planar imaging (EPI) hardware from Advanced NMR (Willmington, Mass., USA). Conventional spin echo sagittal T<sub>1</sub>-weighted (TE = 11 ms, TR = 500 ms, FOV = 24 cm, slice thickness = 5 mm, slice gap = 2.5 mm, 256×128×1 Nex) 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 level 9 ( $z = -8$ ) according to the atlas of Talairach and Tournoux (1988), the middle slice at level 7–8 ( $z = +8$ ) and the superior slice at level 6–7 ( $z = +20$ ). Conventional spin echo images (TE = 11 ms, TR = 500 ms, FOV = 40×40 cm<sup>2</sup>, 256×192×2 Nex) of these slice locations were collected prior to the start of each activation paradigm. These anatomical images were later used as the background images on which to overlay activation maps.

Initial analyses were performed on the data from each subject separately using software written in MATLAB (The MathWorks, Natick, Mass., USA). The activation images were collected using an EPI gradient echo sequence (Flip angle 60°, TE = 45 ms, TR = 1500 ms, FOV = 40×20 cm, 128×128×1 Nex) in the three slice locations described above. Twenty-four images per slice location were collected while the subject performed each of the four tasks (line, case, rhyme or semantic category). With each task run four times, a total of 96 images per slice per task was collected in this study. The first seven images from each series were dropped because they were obtained before a steady state of the echo-planar sequence was obtained.

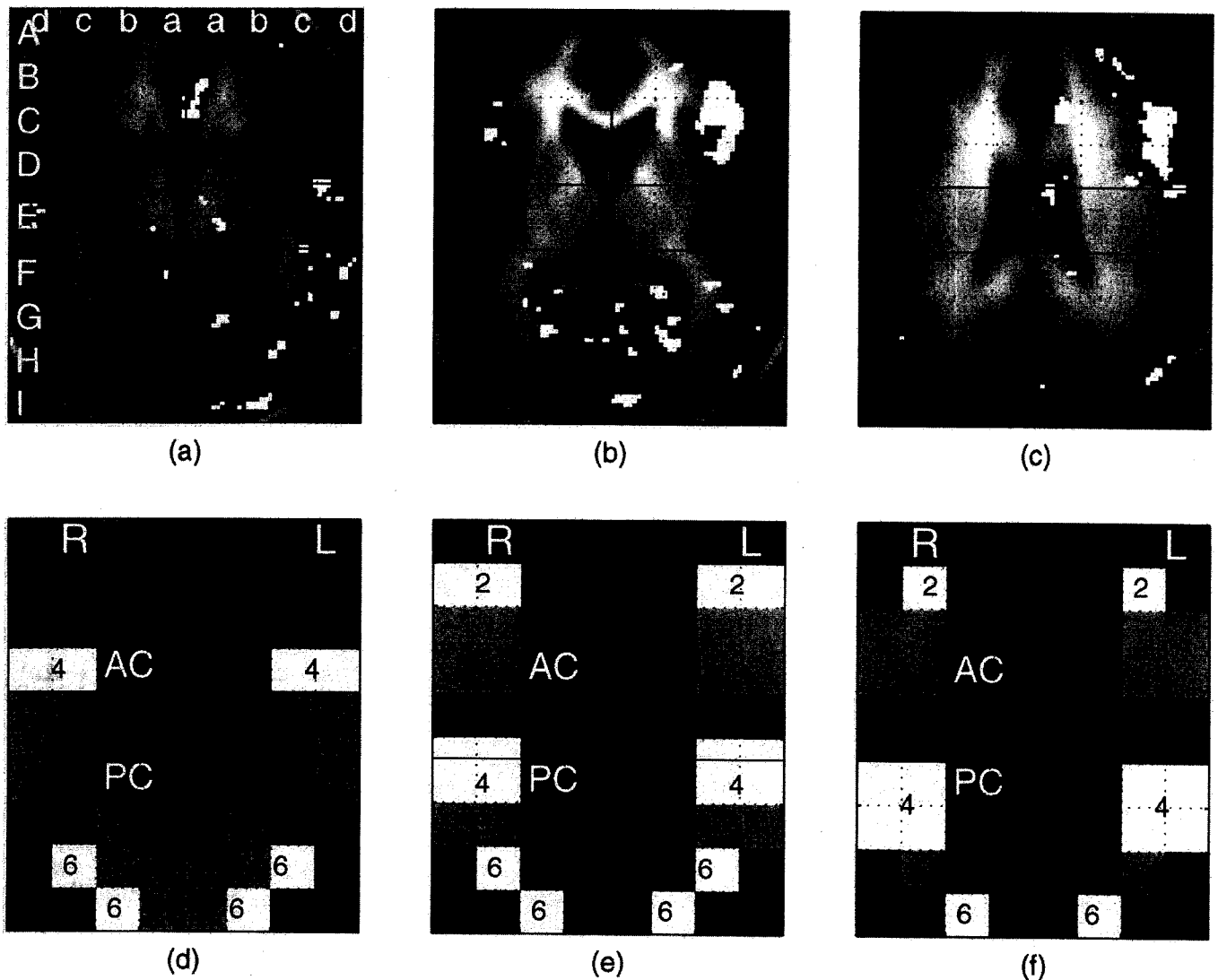
As a first step in data processing, a temporal mean intensity image was formed; this is the mean of all images across all conditions. This image was then subtracted from each individual image, thus generating a large set of difference images. This step is performed in preparation for median filtering as median filtering is more effective on a difference image where it is not corrupted by contrast discontinuities between different tissues. The difference images were then median filtered, i.e. each pixel was replaced by the median of its 3×3 neighborhood; this procedure smoothes images by removing spikes created by machine noise. The overall mean intensity image was then added back to the median

filtered difference images. These two steps provide cleaner data sets by reducing noise that can be associated with the imaging process, thereby making the subsequent  $t$  maps less artifact prone. Subject head movements were analysed but not corrected; when movements were >1 pixel the images were simply discarded and only the movement-free data were analysed. As a final step, activated pixels were detected for each pair of activation tasks (each subtraction condition) using a split Student's  $t$  test. The split  $t$  test divides the data into two parts and performs a separate  $t$  test on each part. If the  $t$  value for a given pixel from both  $t$  maps was >2.0 (with a nominal value of  $P < 0.05$  on each, hence a nominal  $P < 0.0025$  for both) the pixel was considered to be activated. The number of significantly activated pixels in a given ROI was used as the activation score for any given subtraction condition.

For each anatomical image, the positions of the anterior and posterior commissures 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 coregistered to standard Talairach form using cubic proportional fitting (a piece-wise warping algorithm) for each block defined by the anatomical landmarks. This divides the brain into rectangular volumes defined by upper- and lower-case letters and by  $x$ ,  $y$  and  $z$  coordinates. A composite anatomical image for each slice location was obtained by adding Talairach-scaled anatomical images from each of the 38 subjects. Anatomical landmarks were well maintained in the composites. For qualitative analysis, a composite activation image based on the 38 subjects was made for each of the three slice locations and overlaid onto corresponding composite anatomical images. These images revealed areas of consistent activation (mean  $t > 0.5$ ) in the semantic category–line subtraction (Fig. 1).

### Regions of interest

Seven ROI were chosen for analysis in each hemisphere in order to ensure broad coverage of potentially relevant sites (see Table 2). Full extent of ROI was defined by rectangular volumes from the system of Talairach and Tournoux (1988) that encompassed well-established gyral and sulcal patterns and Brodmann areas. The centre of ROI was approximated by coordinates referenced to  $x$ -,  $y$ - and  $z$ -axes (Table 2). The rectangular volumes are large enough to account for anatomical variability between subjects and to insure reproducible coverage of areas of interest in a large number of subjects. Intensity thresholding eliminated spurious activations originating from outside the brain from the statistical analysis. Accordingly, rectangular volumes could be chosen to include areas of peripheral grey matter even though a portion of the volume extended beyond the brain. These ROI are numbered in Fig. 1 as follows: (1) lateral orbital gyrus (with Talairach and Tournoux volume coordinates of



**Fig. 1** Brain activation during semantic task (category–line subtraction). In A–C composite activations (median  $t > 0.5$ ) are superimposed on composite anatomical images. In D–F ROI are shown as defined in Table 2; see text for numerical code and details. AC = anterior commissure; PC = posterior commissure; R = right hemisphere and L = left hemisphere. The Talairach grid system is indicated in each part with dotted lines and labelled in A with upper-case letters (y-axis) and lower-case letters (x-axis). Parts A and D are at  $z = -8$ , B and E are at  $z = 8$  and C and F are at  $z = 20$ . Note activation in the inferior frontal gyrus (Brodmann areas 44 and 45) in B and C, in the superior and middle temporal gyri in A and B, and in the medial and lateral extrastriate areas in A. See Table 2 for list of ROI.

Ab, Bb, Bc, Cb, Cc at  $z = -8$ , Brodmann areas 10 and 47); (2) prefrontal dorsolateral (Bc, Bd at  $z = 8$ , and Bc at  $z = 20$ , encompassing primarily Brodmann Area 46); (3) inferior frontal gyrus (Cc, Cd, Dc, Dd at  $z = 8$ , and Cc, Cd, Dc, Dd at  $z = 20$ , including primarily Brodmann Area 44 and part of 45); (4) superior temporal gyrus [Dc, Dd at  $z = -8$ , E3c, E3d, Fc, Fd at  $z = 8$  (E1 and E2 areas were not used in order to minimize volume averaging with parietal operculum) and Fc, Fd, Gc, Gd at  $z = 20$ , Brodmann areas 22, 38 and 42]; (5) middle temporal gyrus (E1c, E1d, E2c, E2d, E3d, Fd at  $z = -8$ , Gc, Gd at  $z = 8$ , and Hc at  $z = 20$ , Brodmann areas 21, 37, 39); (6) lateral extrastriate (Hc, Ib, at  $z = -8$  and  $z = 8$ , Ib at  $z = 20$ , Brodmann areas 18 and 19); and

(7) medial extrastriate (Gb, Ha, Hb, Ia at  $z = -8$ , Ha, Ia at  $z = 20$ . It should be noted that the names are best approximations.

### Statistical analyses

The first stage of the data analysis, described above, provides activation scores ( $t$  maps) for each subject in every possible subtraction condition (see Table 3). Analyses of variance (ANOVA) were performed on these scores for each ROI. The analyses included the following factors: hemisphere (LH versus RH), subtraction condition (e.g. case–line versus rhyme–case versus semantic category–rhyme) and sex. The

**Table 2** *Regions of interest*

Region	Cortex	Gyrus	Brodmann area	Talairach coordinates* (x/y/z)
(1) Prefrontal lateral-orbital	Prefrontal	Lateral orbital gyrus and inferior aspect of pars orbitalis of inferior frontal gyrus	10	2.5/6.0/-8
			47	5.0/3.5/-8
(2) Prefrontal dorsolateral	Prefrontal	Anterior half of the inferior frontal sulcus, bordered by inferior aspect of middle frontal gyrus and by anterior aspect of pars triangularis of the inferior frontal gyrus	46	4.5/4.5/8.0 5.2/4.0/20
(3) Premotor inferior frontal (centred in Broca's area)	Premotor	Inferior frontal gyrus, pars opercula and all of pars triangularis, except its anterior aspect	44	5.0/2.0/8.0
			45	5.7/1.8/20
(4) Superior temporal	Temporal	Superior temporal gyrus	38	5.4/1.4/-8.0
			42	6.2/-1.1/8.0
			42	6.1/-3.0/20
			22	6.4/-3.8/8.0
			22	6.0/-4.2/20
(5) Middle temporal	Temporal	Middle temporal gyrus	21	6.2/-2.3/-8.0
			21	6.0/-5.2/8.0
			37	5.9/-5.8/-8.0
			39	4.8/-6.8/20
(6) Lateral extrastriate	Visual association	Lateral (middle) and inferior occipital gyri	18	3.8/-8.8/-8.0
			18	2.7/-9.5/8.0
			18	2.1/-9.2/20
			19	4.8/-7.6/-8.0
			19	4.5/-8.0/8.0
(7) Medial extrastriate	Visual association	Medial occipital temporal gyrus and superior aspect of cuneus	18	1.5/-7.8/-8.0
			18	0.2/-8.0/20
			18	2.4/-5.5/-8

\*Approximate centre of region: x coordinates are positive in the RH and negative in the LH; z = -8 is level 9; z = 8 is level 7-8; z = 20 is level 6-7.

**Table 3** *Mean number of pixels by region and subtraction condition*

Region	One-step subtractions			Multi-step subtractions		
	Case-line	Rhyme-case	Sem.-rhyme	Rhyme-line	Sem.-line	Sem.-case
Total area	177.0	250.7	192.1	420.8	574.0	378.8
Lateral extrastriate	14.0	4.3	6.5	19.0	21.6	9.8
Medial extrastriate	6.7	3.9	9.0	9.2	17.2	11.5
Inferior frontal gyrus	7.8	24.7	7.5	31.4	35.8	27.9
Pre-frontal dorsolateral	4.1	15.8	3.5	14.8	16.9	15.0
Lateral orbital	4.9	19.2	7.2	20.9	24.1	22.1
Superior temporal	13.0	15.5	15.8	31.6	47.4	28.2
Middle temporal	16.6	13.3	16.5	28.6	45.3	26.0

Sem. = semantic category.

first two factors were repeated measures variables. The dependent variable was the activation score, i.e. the sum of pixels within these ROI that demonstrated significant positive changes in MR image intensity between the tasks being compared (by split *t* test). Hence, these analyses allowed us to determine whether differences in the mean number of significantly activated pixels for different tasks was reliable

across subjects. [While a pixel-by-pixel analysis is performed for each subject in the first stage (*t* maps) the subsequent analyses of variance determine average task-specific activation differences across subjects in a given region. While, of necessity, this reduces spatial resolution, it is nonetheless the case that the mean differences between tasks within fairly large but coherent regions constitutes a critical

test of the general structure/function relationships to a first approximation. Once structure/function relationships are established for a given region across subjects, more fine-grained investigations of variation among individuals may be of subsequent interest.] By performing an ANOVA on the scores from the preliminary statistical analysis the procedure should substantially reduce the incidence of random error. Results are presented first for the total area scanned, then by ROI. For each region the primary common baseline and one-step results are reported first. Results of relevant converging subtraction analyses are reported to provide further tests of conclusions derived from the primary analyses. [With seven regions analysed and with multiple subtraction analyses employed for each one, the matter of correction for Type I error becomes important. With reference to the primary analyses, given that each region consists of a different data set and given that the dependent variable is already a statistically computed measure (the number of significant pixels), we adopt the standard uncorrected ANOVA model for main effects and simple effects only where significant interactions are obtained in the omnibus analysis. Further, the requirement of the converging subtractions strategy for a logical and consistent pattern of results further mitigates against Type I error. Importantly, given that we require a pattern of both significances and non-significances, the standard Bonferroni correction for multiple analyses is by our view ill suited, since that procedure favours non-significances. Although questions of how to cope most efficiently with Type I error in the case of multiple analyses remain to be resolved, the current set of analyses, in our view, constitute a conservative and multi-faceted procedure for establishing reliable structure/function relationships.] Relevant sex differences are reported fully at the end of each section and also mentioned during the discussion of main effects.

## Results

### Total area

This initial analysis measured total activation across all scanned areas for both the RH and LH separately. This analysis provides information regarding overall activation differences among subtraction conditions by sex or by hemisphere which are not limited to the pre-defined ROI. It provides the foundation for interpreting more fine grained differences across regions.

In the common baseline subtraction condition analysis (case-line, rhyme-line and semantic category-line) a main effect of subtraction condition was observed [ $F(2,36) = 15.93, P < 0.001$ ] (for all subsequent analyses in the results section refer to Table 3 for the appropriate means). Separate contrasts revealed that rhyme-line produced greater activation than case-line [ $F(1,36) = 11.80, P < 0.01$ ]. Similarly, semantic category-line resulted in significantly greater activation than rhyme-line [ $F(1,36) = 4.67, P < 0.05$ ] (but see below for a qualification of each effect by sex). An effect

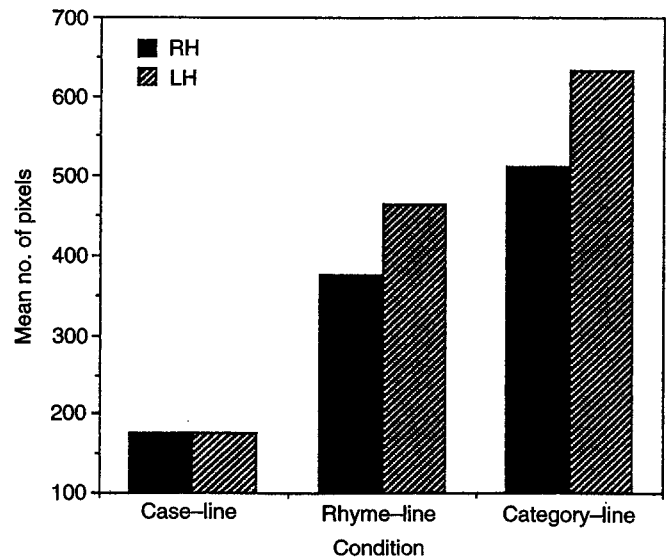


Fig. 2 Mean number of activated pixels by hemisphere and subtraction condition across all regions scanned.

of hemisphere was obtained [ $F(1,36) = 7.74, P < 0.01$ ] but this was qualified by an interaction with subtraction condition [ $F(2,72) = 5.08, P < 0.01$ ]. As shown in Fig. 2 the case-line subtraction was associated with equivalent RH and LH activation, while rhyme-line and semantic category-line subtractions were associated with greater activation in the LH. No effects of subtraction condition were obtained in the one-step analysis (case-line, rhyme-case, semantic category-rhyme).

**Converging subtractions.** When the line task was employed as the common baseline we obtained increased activation from case to rhyme to semantic category. To address the question of whether this pattern might be attributed to some unknown artifact associated with the use of the line task as a control we next contrasted the rhyme-case versus semantic category-case subtractions (see Table 1 for rationale). A reliable difference was obtained [ $F(1,36) = 10.42, P < 0.01$ ] (note in Table 3 the mean rhyme-case = 250.7 and mean semantic category-case = 378.8).

**Sex differences in total area analyses.** Two major sex differences were observed in the total area analyses. In the common baseline analysis a marginal subtraction condition $\times$ sex interaction was obtained [ $F(2,72) = 2.94, P = 0.059$ ] (see Fig. 3). For males the means for case-line, rhyme-line and semantic category-line conditions were 188.8, 418.8 and 727.5 (each of the differences were reliable), while for females the corresponding means were 165.2, 422.7 and 420.6, respectively. In summary, females did not show an increase in the numbers of activated pixels from the rhyme to semantic category subtractions while males did. A sex $\times$ hemisphere interaction was observed in both the common baseline analysis [ $F(1,36) = 7.61, P < 0.01$ ] and in the one-step analysis [ $F(1,36) = 7.09, P < 0.025$ ]. The



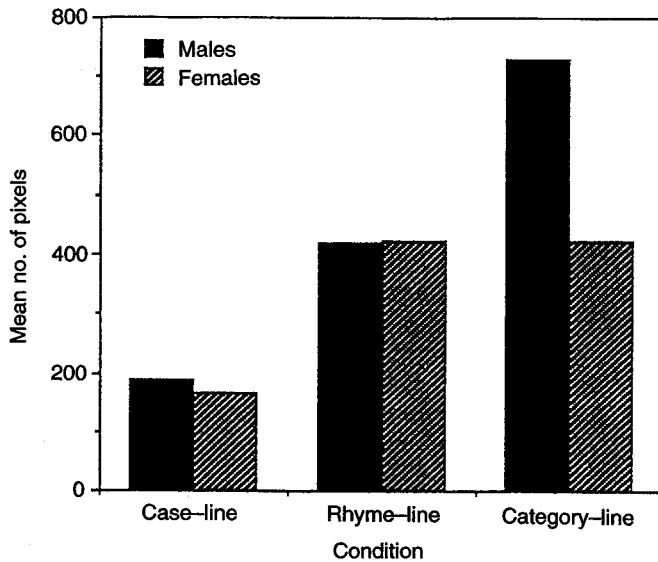


Fig. 3 Mean number of activated pixels by sex and subtraction condition across all regions scanned.

RH and LH means in the common baseline analysis were for males, 374.8 and 515.1, while for females the corresponding means were 335.8 and 336.5. Thus, females showed equivalent LH and RH activation, while males displayed greater activation in the LH.

### Occipital regions

Two occipital ROI were examined: the lateral extrastriate and medial extrastriate regions.

#### Lateral extrastriate area

In this region the common baseline condition analysis (case-line, rhyme-line and semantic category-line) revealed no significant effects of subtraction condition; all three subtractions differed on the orthographic dimension (see Table 3). By contrast, the one-step subtraction (case-line, rhyme-case and semantic category-rhyme) analysis revealed a significant main effect of subtraction condition [ $F(2,72) = 5.49, P < 0.01$ ] (see Table 3). [Although there was a good deal of variability in the numbers of pixels activated by different subjects and, although the mean number of pixels activated is occasionally small, the repeated measures ANOVA allows us to determine whether the differences between tasks are stable across subjects. Hence, obtaining a statistically robust effect, in spite of relatively small means and small mean differences, indicates that the difference favouring a given task was consistent across the 38 subjects. (One subject might have means of 4 and 8 pixels in two tasks, while another might have means of 16 and 32 pixels. Robust  $F$  values indicate that few, if any subjects reversed that pattern).] Separate analyses revealed that case-line was associated with significantly more activated pixels than both rhyme-case [ $F(1,72) = 9.98, P < 0.01$ ] and semantic

category-rhyme [ $F(1,72) = 5.96, P < 0.025$ ], while rhyme-case and semantic category-rhyme did not differ ( $F < 1.0$ ).

*Converging subtractions.* Thus, for the one-step subtractions, in the condition where the tasks differed on an orthographic dimension (case-line), significant increases in the number of activated pixels were seen relative to conditions where orthographic processing was present in both tasks (rhyme-case or semantic category-rhyme). Further, in the common baseline condition where all tasks differed on an orthographic dimension, no reliable differences were found. This would suggest that the lateral extrastriate region is most strongly associated with orthographic processing. If so, then other comparisons should converge on the same conclusion (see Table 1). To test this hypothesis, we contrasted the rhyme-case and the rhyme-line subtractions. By the logic of the design, in the former subtraction the tasks differed only on the phonological dimension, while in the latter subtraction the tasks differed on both orthographic and phonological dimensions. Therefore a significant difference, favouring the rhyme-line condition, should be observed in this region since the rhyme-line should isolate orthography while rhyme-case should not. As expected a significant difference between the two subtractions was obtained [ $F(1,36) = 10.28, P < 0.01$ ] (see Table 3).

By the same reasoning, a comparison between semantic category-case and semantic category-line should produce increased activation for the latter condition since only in this subtraction do the experimental and control tasks differ on an orthographic dimension. As expected a significant difference was observed [ $F(1,36) = 7.46, P < 0.01$ ]. In summary, for those subtraction conditions where the experimental task differed from the control in terms of orthographic demands (i.e. when the line task was used as a baseline) significantly greater activation was observed relative to all other comparisons where the cognitive difference between the two tasks was other than orthographic.

#### Medial extrastriate

In contrast to the analyses involving the lateral extrastriate region, a somewhat different pattern of results was obtained for the medial extrastriate region. A significant effect of subtraction condition was obtained in the common baseline analysis [ $F(2,72) = 5.86, P < 0.01$ ]. Separate contrasts revealed that semantic category-line was associated with significantly greater activation than either rhyme-line [ $F(1,72) = 6.24, P < 0.025$ ] or case-line [ $F(1,72) = 10.74, P < 0.01$ ], while rhyme-line and case-line did not differ ( $F < 1.0$ ) (however, see below for a relevant sex difference). The one-step analysis revealed no effects of subtraction condition or any interactions.

*Converging subtractions.* The key result from the primary analysis in the common baseline condition was that processing in the semantic category task was associated with

greater activation than either the case or rhyme tasks. To examine this effect using a different baseline we contrasted rhyme–case with semantic category–case subtraction conditions. In this analysis a significant semantic category–case advantage was seen [ $F(1,36) = 6.92, P < 0.025$ ]. Thus, processing real words activated this region to a greater degree than processing pronounceable nonwords. The differing patterns of activation obtained across logically comparable subtractions suggests a functional difference between the lateral and medial aspects of the extrastriate cortex.

**Sex differences in lateral and medial extrastriate regions.** In the common baseline analysis for the medial extrastriate region a subtraction condition by sex interaction was obtained [ $F(2,72) = 3.25, P < 0.05$ ]. Whereas males showed the pattern of increased activation in the semantic category–line (24.1) relative to the rhyme–line (8.2) or case–line (7.6) conditions, females showed no increase in semantic category–line (10.3) relative to rhyme–line (10.1) or case–line (5.7). A similar interaction between subtraction condition and sex was also seen in the lateral region [ $F(2,72) = 4.81, P < 0.05$ ]. In summary, in extrastriate regions (as in the total area analysis) females fail to show patterns of increased activation for real words (semantic category–line) relative to nonwords (rhyme–line) while males do show them.

## Frontal regions

### Inferior frontal gyrus

In the common baseline subtraction several effects and interactions were observed in the region consisting of Brodmann areas 44 and 45. First, a main effect of subtraction condition was obtained [ $F(2,72) = 12.76, P < 0.001$ ]. Contrasts indicated that both rhyme–line [ $F(1,72) = 15.70, P < 0.001$ ] and semantic category–line [ $F(1,72) = 22.05, P < 0.001$ ] differed significantly from case–line. However, semantic category–line and rhyme–line did not differ ( $F < 1.0$ ). A main effect of hemisphere was obtained as well [ $F(1,36) = 10.65, P < 0.01$ ] indicating greater LH (32.1) than RH (17.9) activation (however, see below for an interaction with sex). Subtraction condition and hemisphere interacted significantly [ $F(2,72) = 3.40, P < 0.05$ ]. The means for case–line, rhyme–line and semantic category–line subtractions for the RH were 5.1, 20.5 and 28.0, respectively, while the corresponding LH values were 10.5, 42.4 and 43.6, respectively.

The one-step subtractions revealed a main effect of subtraction condition [ $F(2,72) = 10.75, P < 0.001$ ]. Rhyme–case significantly differed from both case–line [ $F(1,72) = 15.85, P < 0.001$ ] and semantic category–rhyme [ $F(1,72) = 16.40, P < 0.001$ ] while case–line and semantic category–rhyme did not differ significantly ( $F < 1.0$ ). As in the common baseline analysis, there was an effect of hemisphere [ $F(1,36) = 9.65, P < 0.01$ ] with means of 10.3 and 16.4 in the RH and LH (again qualified by sex, as discussed below).

**Converging subtractions.** It will be recalled that in the lateral extrastriate region rhyme–case produced significantly less activation than rhyme–line, presumably due to the fact that the latter condition differed in orthography (as well as phonology) while the former differed only on the phonological dimension. That result was consistent with the conclusion that the lateral extrastriate region is primarily associated with orthographic processing. If the inferior frontal gyrus is associated with phonological processing but not with orthographic processing, then the rhyme–case and rhyme–line comparison should yield no difference since both subtractions differ on a phonological dimension. However the mean number of pixels should be relatively large in both. As expected, no main effect of task was observed in this analysis ( $P > 0.25$ ) yet the mean values were high.

In the common baseline analysis we found no indication that semantic category judgements resulted in increases in activation relative to the rhyme task. To confirm this, we also contrasted the rhyme–case and semantic category–case subtractions. Both rhyme and semantic category differ from case on a phonological dimension; the only difference is that the latter subtraction also differs on a semantic dimension. As in the common baseline analysis, no difference was observed between semantic category and rhyme ( $F < 1.0$ ).

Although the preceding analyses indicate that semantic processing was not associated with increased activation in the inferior frontal gyrus relative to rhyming, it is nonetheless true that a strong activation was obtained not only in the nonsense word rhyme judgement, but also with the real word stimuli in category judgement. To test for the possibility that the phonological processing associated with word stimuli in the semantic category task was the basis for observed activation we contrasted the semantic category–case with the semantic category–rhyme subtractions. Note that while both subtractions differ on the semantic dimension, only the former differs on a phonological dimension (since both rhyme and semantic tasks engage phonological processing). Assuming that phonological processing makes heaviest demands on this region, we expect an advantage for the former subtraction. As expected, a significant main effect of task was obtained [ $F(1,36) = 13.72, P < 0.001$ ].

### Lateral orbital gyrus

In the common baseline condition a main effect of subtraction condition was obtained [ $F(2,72) = 16.43, P < 0.001$ ]. Separate contrasts revealed that relative to the case–line condition both rhyme–line [ $F(1,72) = 19.88, P < 0.001$ ] and semantic category–line conditions [ $F(1,72) = 28.62, P < 0.001$ ] produced reliably greater activation. Rhyme and semantic category, however, did not differ significantly ( $F < 1.0$ ). No other effects or interactions were significant.

Once again in the one-step subtraction, a main effect was found [ $F(2,72) = 7.28, P < 0.01$ ]. Rhyme–case differed significantly from both the case–line [ $F(1,72) = 12.61, P < 0.001$ ] and semantic category–rhyme conditions

[ $F(1,72) = 8.92, P < 0.01$ ] while case–line and semantic–rhyme did not differ ( $F < 1.0$ ). Thus, as in the common baseline subtraction, we may suppose that this region serves primarily a phonological function; no evidence was obtained for semantic effects, above and beyond the phonology.

**Converging subtractions.** To confirm that there was no activation uniquely associated with orthographic processing in the lateral orbital region we contrasted the rhyme–case and rhyme–line subtractions. Again, rhyme differs from both case and line on the phonological dimension (hence the mean number of pixels activated should be large), but the fact that rhyme–line also isolates orthography while rhyme–case does not should have no effect. As anticipated, we found no difference between rhyme–case and rhyme–line ( $F < 1.0$ ). Similarly, in order to confirm that there were no activation increases associated with semantic processing in this region we contrasted rhyme–case with semantic category–case. As expected no significant differences were observed ( $F < 2.0$ ). By contrast, when we compared semantic category–case with semantic category–rhyme we expected to obtain a difference since only the former subtraction isolates phonology. Consistent with this we found an effect of task [ $F(1,36) = 13.47, P < 0.001$ ].

### *Pre-frontal dorsolateral region*

In the common baseline analysis a main effect of subtraction condition was obtained [ $F(2,72) = 12.27, P < 0.001$ ]. Separate analyses revealed that in contrast to case–line both rhyme–line [ $F(1,72) = 14.85, P < 0.001$ ] and semantic category–line [ $F(1,72) = 21.39, P < 0.001$ ] produced greater activation. However, semantic category–line did not differ significantly from rhyme–line ( $F < 1.0$ ).

In the one-step subtraction, there was a main effect of subtraction condition [ $F(2,72) = 9.49, P < 0.001$ ]. Contrasts indicated that rhyme–case differed from both case–line [ $F(1,72) = 13.56, P < 0.001$ ] and semantic category–rhyme [ $F(1,72) = 14.88, P < 0.001$ ]. Thus, by this analysis it appears that phonological processing makes somewhat greater demands on the region than semantic processing.

**Converging subtractions.** Rhyme and semantic category were next contrasted with an alternative baseline, the case task. If semantic processing makes greater demands on this region then the semantic category–case subtraction should yield greater activation than rhyme–case. No main effect of subtraction condition was observed ( $F < 1.0$ ). Further, rhyme–line versus rhyme–case did not differ ( $F < 1.0$ ) suggesting no role for orthographic coding in this region. However, as at other frontal sites, semantic category–case produced greater activation than semantic category–rhyme [ $F(1,36) = 12.62, P < 0.01$ ] indicating a strong phonological role for the prefrontal dorsolateral region. In short, the pattern of results closely resembles what was obtained at other frontal sites.

**Sex differences in frontal regions.** Sex differences in the inferior frontal gyrus were initially reported and discussed in Shaywitz *et al.* (1995b). In the one-step subtraction analysis, hemisphere interacted with sex [ $F(1,36) = 14.14, P < 0.001$ ]. The RH and LH means (collapsed across tasks since there was no higher order interactions) were 6.0 versus 19.5 for males and 14.5 versus 13.3 for females. The effect of hemisphere was significant for males [ $F(1,18) = 19.09, P < 0.001$ ] but not for females ( $F < 1.0$ ). Further, as noted above, the rhyme–case subtraction produced reliably stronger activation than either case–line or semantic category–rhyme.

In the common baseline subtraction a similar interaction was observed. A sex  $\times$  hemisphere interaction was found [ $F(1,36) = 5.9, P < 0.025$ ]. The overall means for the RH and LH were 17.4 and 42.3 for males and 18.4 and 22.0 for females. Separate analyses for males and females confirm that males showed greater LH activation [ $F(1,18) = 17.47, P < 0.001$ ], while females did not ( $F < 1.0$ ).

To explore this sex difference further we examined the ratio of RH to LH activation in the inferior frontal gyrus. Eleven of 19 females, but no males had an RH/LH ratio  $\geq 0.70$ ; in fact for nine of these 11 females the RH/LH ratio was  $\geq 1.0$ . Thus, more than half of the female subjects produced strong bilateral activation in the inferior frontal gyrus; by contrast, no males showed this pattern.

Although sex differences in regard to lateralization were most pronounced in the inferior frontal gyrus, further analyses also indicated a similar pattern in the orbital gyrus as well. In this latter region, which was most strongly associated with phonological processing, greater LH than RH activation was seen in males. The means for the rhyme–line subtraction were 14.8 and 23.6 in the RH and LH hemispheres, and the difference was significant [ $F(1,18) = 5.52, P < 0.05$ ]. For female subjects the corresponding means of 24.5 and 20.9, respectively, were not significantly different ( $F < 1.0$ ). In the pre-frontal dorsolateral region a similar pattern was seen. The means for males were 10.8 and 16.8 while the corresponding means for females were 16.9 and 14.5, but neither difference was significant.

## *Temporal regions*

### *Middle temporal gyrus*

In the common baseline condition a significant main effect of subtraction condition was observed [ $F(2,72) = 10.44, P < 0.001$ ]. Rhyme–line differed marginally from case–line [ $F(1,72) = 3.6, P = 0.06$ ] and semantic category–line differed from case–line [ $F(1,72) = 20.70, P < 0.001$ ]. Interestingly, semantic category–line also differed from rhyme–line [ $F(1,72) = 7.02, P < 0.01$ ] (though *see* below for qualification by sex). In the one-step subtraction no main effect of subtraction condition was found ( $F < 1.0$ ). Note, however, that high mean values in each subtraction were found for this region relative to frontal and occipital regions.

*Converging subtractions.* If, as suggested by the common baseline analyses, the combined phonological and semantic processing entailed in the semantic category–line subtraction activates the middle temporal region more broadly than does phonological processing in the rhyme–line subtraction, then this pattern should hold in other logical subtractions. For instance, if we compare the rhyme–case (phonology) with the semantic category–case (phonology+semantic) we should observe stronger activation in the latter contrast (and this would contrast with frontal sites where no differences were observed in this comparison). As expected a significant difference was observed [ $F(1,36) = 11.76, P < 0.01$ ]. Hence, as in the common baseline subtraction, semantic judgements produced greater activation, on average, than did rhyme judgements.

### *Superior temporal gyrus*

(We note that anterior and posterior aspects of this region are distinguished in the three slices. We did not observe any relevant interactions with slice, hence this factor is not included in these results.) The common baseline analysis revealed a significant main effect of subtraction condition [ $F(2,72) = 13.21, P < 0.001$ ]. Subsequent analyses indicated that rhyme–line produced reliably greater activation than case–line [ $F(1,72) = 7.69, P < 0.01$ ] and that semantic category–line produced reliably greater activation than case–line [ $F(1,72) = 26.36, P < 0.001$ ]. However, as in the middle temporal region, semantic category–line produced greater activation than rhyme–line [ $F(1,72) = 5.57, P < 0.025$ ] (but *see* below for relevant sex differences). The one-step subtraction analysis revealed no effects of subtraction condition ( $F < 1.0$ ), although means were high for each.

*Converging subtractions.* Again, if phonological plus semantic processing does indeed make greater demands on this region than phonological processing alone, this should be evident in the rhyme–case and semantic category–case comparison (as seen in the middle temporal gyrus analysis). As expected semantic category–case resulted in reliably greater activation than did rhyme–case [ $F(1,36) = 15.67, P < 0.001$ ].

*Sex differences in temporal regions.* The increased activation in the semantic category task in the common baseline subtraction in the middle temporal gyrus was qualified by a subtraction condition by sex interaction [ $F(2,72) = 3.87, P < 0.05$ ]. The means for the case–line, rhyme–line and semantic category–line subtractions were, for males 14.7, 30.1 and 60.2, respectively, and for females the means were 18.4, 27.1 and 30.6, respectively. Separate analyses indicated that for males the semantic category–line condition made significantly greater demands on this region than rhyme–line [ $F(1,36) = 7.85, P < 0.01$ ] while for females rhyme–line and semantic category–line did not differ ( $F < 1.0$ ). Similarly, in the case baseline analysis (rhyme–

case versus semantic category–case) the subtraction condition by sex interaction was significant [ $F(1,36) = 4.04, P = 0.05$ ]. For males the means for rhyme–case and semantic category–case were 16.6 and 36.6, respectively, and for females the corresponding means were 10.1 and 15.3, respectively. Hence, in both converging subtractions, increases in the number of activated pixels in the semantic category task relative to the rhyme task were obtained, but only for male subjects.

The results for the superior temporal gyrus were similar. Subtraction condition interacted with sex in the common baseline subtraction [ $F(2,72) = 3.34, P < 0.05$ ]. For males, the means for the case–line, rhyme–line and semantic category–line were 17.1, 34.5 and 65.9. In contrast, the corresponding means for females were 8.8, 28.6 and 28.9. Similarly, in the rhyme–case versus semantic category–case converging subtraction, a similar subtraction condition by sex interaction was observed [ $F(1,36) = 8.45, P < 0.01$ ]. The means for the rhyme and semantic category conditions were 12.7 and 34.9, respectively, for males, and 18.1 and 21.5, respectively, for females. Thus, as in the middle temporal gyrus, the increased activity associated with semantic processing in the superior temporal region appears to be sex dependent, present in males but not in females.

## Discussion

The use of subtraction paradigms to isolate specific brain foci has been much criticized recently for reasons we have indicated (Sergent, *et al.*, 1992; Friston, *et al.*, 1993). Criticisms have been made regarding the tentative nature of the assumptions of pure insertion and deletion, as well as the problem of spurious differences between experimental and control tasks. The experimental paradigm employed in the present study allowed us to isolate regions most strongly associated with orthographic (letter) processing, phonological processing and lexical–semantic processing using multiple subtractions (in most cases with different experimental and control tasks). This greatly increased our confidence in subsequent conclusions regarding structure/function relationships. The four tasks had a common structure: comparable judgements (matched versus different) and response execution (bulb press) components. They differed primarily in the level of linguistic information required to make the judgement. The consistency of the results across these subtractions is gratifying; coherent patterns of significances and non-significances were observed in each region. Had any of the activation results from the primary analyses been purely artifactual we would surely not have found such consistency across subtractions. We illustrate this in the following discussion.

With regard to the primary findings from this experiment, the initial analysis of total area scanned sets the stage for interpretation of the distinct patterns observed in each ROI. Two primary findings emerged from this overall analysis. First, in the common baseline condition, a systematic increase

in the number of activated pixels was observed from the case–line subtraction to the rhyme–line subtraction and from this subtraction to semantic category–line subtraction. This pattern of activation is consistent with the expectations from the cognitive assumption that each subsequent task adds operations not required by the previous tasks. A converging subtraction (rhyme–case and semantic category–case) showed a similar increase from rhyming to semantic category judgements. Second, in this analysis a subtraction condition by hemisphere interaction indicated that subtractions which engaged phonological processing (rhyme–line and semantic category–line) showed a LH advantage, whereas the purely orthographic subtraction (case–line) was associated with equivalent LH and RH activation. Each of these findings was in turn qualified by the sex of the subject as discussed below.

In the separate analyses pertaining to ROI, we observed differences in the patterns of results across subtraction conditions between occipital, temporal and frontal regions. While the patterns of results are complex, we believe that they lend themselves to the following summary. The lateral extrastriate region appears most strongly associated with orthographic processing, the medial extrastriate region, by contrast, was more responsive to real words, than to nonword strings of letters. The frontal regions were most strongly associated with phonological processing; no unequivocal evidence of either orthographic or semantic processing was observed. Finally, temporal regions appeared to be multifunctional, strongly activated, but to differing degrees, by phonological and semantic processing.

We must emphasize, however, that several regions of perhaps equal interest could not be scanned in this experiment (limitations on data acquisition and storage at the time the study was conducted limited us to three slices; however, we attempted to cover the maximum number of potentially relevant sites that three slices could encompass). The supramarginal gyrus, to mention one such area, has been shown to be relevant to phonological processing (Paulesu *et al.*, 1993; Demonet *et al.*, 1994) but we could not include it in the current slice locations. We therefore make no claim to have exhausted the regions of relevance in this study. Similarly, the angular gyrus and the lingual gyrus are cortical sites where lesions have been shown to result in pure alexia and alexia without agraphia (Henderson, 1986) and these regions would be relevant to orthographic processing, but could not be investigated in the slices used in the present study. We must therefore await further studies to determine how each of these regions might respond to the sorts of tasks employed here.

### **Orthographic processing**

The lateral extrastriate region appeared to be the one most associated with orthographic processing. In the one-step subtractions this region was more strongly activated in the orthographic subtraction (case–line) than in either the phonological subtraction (rhyme–case) or in the semantic

subtraction (semantic category–rhyme). Common baseline analyses indicated a similar degree of activation for consonant strings, pronounceable nonwords and words. Critically, when both the experimental and control tasks engaged orthography (e.g. rhyme–case, semantic category–case, or semantic category–rhyme) activation was weak, but when the control task did not engage orthography (case–line, rhyme–line, or semantic category–line) activation was strong and was at a comparable level for each type of letter string. We cannot completely rule out the possibility that the letter stimuli engaged more complex visual processing (e.g. different types of eye movements and/or featural processing) than line stimuli which could also be a factor influencing lateral activation. However, complex feature integration is precisely the operation that is assumed to be the core of letter perception (Johnson and Pugh, 1994).

The pattern of results obtained for the medial extrastriate region differed somewhat. In the common baseline analysis a reliable increase in activation was observed for the semantic category–line condition relative to both the rhyme–line and case–line conditions. Further, this pattern was found in the converging subtraction which contrasted rhyme–case with semantic category–case (the qualification of this result by sex is considered below). It would appear that, in general, real words activate the medial extrastriate region more substantially than either consonant strings or pronounceable nonwords.

The finding that orthographic processing makes maximum demands on lateral extrastriate sites is broadly consistent the results of lesion studies (Henderson, 1986) and with conclusions of Petersen and his colleagues (Petersen *et al.*, 1989; Petersen and Fiez, 1993) using different tasks in several PET studies. Petersen *et al.* (1989) examined passive processing of word, pseudoword and consonant string displays with a fixation point baseline and found LH and RH lateral extrastriate activation for all stimuli, but stronger medial activation for pronounceable strings including real words. The results of the present study concur. As noted, we found a response to orthography in the lateral sites but in the medial extrastriate region real word stimuli (in the common baseline subtractions) activated this region to a greater degree (for males) than either consonant strings or pronounceable nonword strings. This dissociation between lateral and medial sites is consistent with Petersen's conclusion (Petersen *et al.*, 1990) that lateral sites are associated with letter processing while medial sites are associated with word form representations. It should be noted that Price *et al.* (1994) did not observe similar medial extrastriate activation when words were contrasted with false font stimuli in several reading tasks. Petersen *et al.* (1990) did not use a false font control; instead they used a passive fixation control in their study. These task differences might be relevant to the contrasting results. In any case, the present experiment finds activation greater for words than nonwords in the medial extrastriate when both are contrasted either with line or consonant string judgements. Given these differences

across studies it will be important to investigate, more fully, the role of this site across different letter processing tasks.

### ***Phonological processing***

The nonword rhyme judgement task forces subjects to explicitly use their knowledge of grapheme-phoneme correspondences in order to generate phonological representations. We acknowledge that the rhyming task itself may engage operations beyond those that are essential in assembling phonological representations in word identification. Hence certain activations could be task specific while others must certainly reflect what we intend to measure, namely phonological assembly. In any event, phonological processing, across subtractions made strong demands on a wide number of sites within both the frontal and the temporal regions. However, the patterns of results in these two broadly defined regions were somewhat different. Within the frontal cortex the lateral orbital, prefrontal dorsolateral and inferior frontal gyrus were associated with reliably greater activation in the rhyme–case relative to either the case–line or semantic category–rhyme subtractions. Common baseline analyses revealed greater rhyme–line than case–line activation but equivalent rhyme–line and semantic category–line results. The converging subtractions further showed minimal activation in those regions that isolated lexical–semantic processing (e.g. semantic category–rhyme as compared with semantic category–case). In short, only when the experimental and baseline tasks differed on a phonological dimension were strong activation patterns observed.

As we noted, the activation of these frontal regions does not seem to be limited to nonword rhyming; equivalent activation was also observed for words in the semantic category task when control tasks not engaging phonology were employed. The interpretation we presently favour is that the frontal activation on word trials should not be attributed to the semantic demands of that task; it may well be a consequence of the phonological processing engaged by these stimuli. First, consider that the semantic category–rhyme subtraction, which logically isolates semantic processing, resulted in significantly less activation than rhyme–case which isolates phonology. Secondly, semantic category–case and semantic-category–line both logically differ on phonological as well as semantic dimensions; these subtractions were associated with significantly greater activation than semantic category–rhyme which should differ on the semantic dimension only (further activation in this subtraction was, in absolute value, quite low). Thirdly, when rhyme–line or rhyme–case subtractions are directly compared with related semantic category–line or semantic category–case subtractions no differences in the numbers of activated pixels are found (this pattern is distinct from that observed in the temporal regions, at least for males, where semantic demands increased the activation scores above and beyond the rhyme comparisons).

In total, these results suggest to us that the phonological

processing engaged during real word reading (as well as for nonword rhyming) is largely responsible for the activation at frontal sites. In this regard, it might have been expected on dual-coding models that nonwords would engage assembled phonological processing much more intensively than would real words (Coltheart *et al.*, 1993) resulting in stronger activation in the rhyme–line than the semantic category–line subtractions in these regions, for example. It should be noted that this did not occur at any site examined in this study. A possible explanation comes from a growing body of research within the behavioural literature that suggests that even at the earliest stages, assembled phonological processing provides a strong constraint on lexical access for real word stimuli (see Van Orden *et al.*, 1990; Lukatela and Turvey, 1991, 1993; Perfetti and Bell, 1991). The fact is that across the frontal sites activated by nonwords in the rhyming task, activation associated with real word processing was similar in magnitude and yet it cannot easily be attributed to the semantic demands of the task. This suggests that we must re-examine certain assumptions made by dual coding models of reading.

However, while our preferred interpretation of the current results is that the frontal sites are most associated with phonological coding and not with semantic coding, we must acknowledge limitations of the current study in this regard. If there were specific networks within these frontal regions that were specifically associated with semantic coding and if these were either very close to, or overlapping with, phonologically related networks then with the given limitations on spatial resolution in fMRI we might not be able to discriminate between them. Thus, while the pattern of results across subtractions clearly implicate a strong role in phonological processing for these regions, we cannot claim that semantic coding (or even orthographic coding) makes absolutely no demands on these regions.

Further, we may ask whether the activation of the inferior frontal gyrus and other frontal sites simply reflects implicit short-term memory demands when pairs of verbal stimuli are presented, i.e. whether it perhaps bears no specific relationship to assembled phonological processing. Activation in the inferior frontal gyrus, which includes Broca's area (encompassing Brodmann areas 44 and 45) has in fact been observed in verbal short term memory tasks by Paulesu *et al.* (1993). However, they found similar activation in both short term memory conditions and in simple rhyming conditions and therefore argued that this inferior frontal activation reflects the operations engaged by sub-vocal rehearsal processes in memory as well as by general phonological processing systems (Paulesu *et al.*, 1993). Like them, we assume that this system is relevant both to assembling a phonological representation from print and to transferring this information into short-term store.

It must be pointed out that aspects of the present findings strongly mitigate against a pure memory account. First, all four tasks involved simultaneous presentation of the two displays; hence they are not explicitly tapping short-term

memory (no retention interval is involved). Secondly, sites within the inferior frontal gyrus have been implicated in tasks that should, in principle, be only minimally associated with short-term memory. Inferior frontal gyrus activation has been seen in speech production tasks (Petersen *et al.*, 1989), and in complex phonetic discrimination of speech tokens (Demonet *et al.*, 1992, 1994; Zatorre *et al.*, 1992), also with phonological judgements on visually presented single letter displays (Sergent *et al.*, 1992), word/nonword discriminations on visual stimuli (Price *et al.*, 1993, 1994) and also, critically, in passive reading of printed words (Price *et al.*, 1994). Moreover, patients with lesions in this region show evidence of difficulties with phonetic discriminations (Blumstein *et al.*, 1977). Also, like Price *et al.* (1994), we recently completed a study using a word/nonword discrimination task on visually displayed letter strings and found strong activation in this region, even though the use of single displays should minimize the memory component (K. R. Pugh *et al.*, unpublished observations). Further, we found that patterns of activation in this region were strongly associated with the magnitude of phonological effects in reading tasks performed out of magnet.

While all of this evidence supports a role for the inferior frontal gyrus in phonological processing and phonological deficit in speech and reading, it must be noted that other frontal sites active in the present experiment, such as the orbital gyrus and the prefrontal dorsolateral region, do not have a such a clearly established links. We must acknowledge, therefore, the possibility that activation at these sites may be somewhat task specific, perhaps related to tacit memory, or specific coding demands specific to the current set of tasks and subtractions. Notwithstanding this, the link between phonological processing and the inferior frontal gyrus is both strong in the present study and entirely consistent with previous studies.

The fact that the inferior frontal gyrus responds to tasks which involve monitoring speech for target phonemes is entirely compatible with the present finding that this site is critically involved in mapping from orthography to phonology in reading. Making phonetic judgements in speech involves cognitive operations on spoken language representations that are smaller than the whole word (sub-lexical phonetic units). Mapping from letters or letter clusters to phonemes or phoneme clusters likewise engages sub-lexical processing. This frontal region thus appears to be a candidate site for this type of mapping. The efficiency with which this mapping is accomplished in reading has been shown to be highly predictive of overall reading ability (Shankweiler *et al.*, 1979; Liberman and Liberman, 1992) and we are currently examining dyslexic readers on these tasks in order to uncover any differences in patterns of activation in this region.

It is evident that the middle and superior temporal gyri display phonological involvement as well. However, the pattern of results across subtractions differed from that obtained at frontal sites. First, there was no evidence in the one-step subtractions that rhyme-case differed from either case-line or semantic category-rhyme as was observed at

frontal sites. Nonetheless, activation was strong in all three subtractions relative to other regions. The common baseline results suggest why this is so. There were reliable increases from case-line to rhyme-line and from rhyme-line to semantic category-line (for males). Thus across one step subtractions activation tends to be high but equivalent for each dimension. It appears that the temporal sites we examined are multi-functional. These sites appear to contain structures relevant to all three types of processing.

### *Semantic processing*

We may infer from the present results that there are sites specialized for semantic processing in both the middle and superior temporal gyri. There were reliable and substantial increases in the numbers of activated pixels from the rhyme-line (or rhyme-case) to the semantic category-line (or semantic category-case) subtraction conditions for males. These increases imply that engaging semantic information necessary for the category judgements does indeed activate networks not engaged by rhyming alone though, as noted, rhyming itself activated the region to a greater degree than case judgements. There have been a number of supportive results from PET and, more recently, from fMRI studies (Wise *et al.*, 1991; Demonet *et al.*, 1992; Shaywitz *et al.*, 1995a). For example, Demonet *et al.* (1992) reported significant increases in activation at a number of sites across the left inferior, middle and superior temporal gyri, as well as the right middle temporal gyrus associated with performing a task in which subjects monitored spoken word pairs for targeted semantic attributes. Although a phoneme monitoring task also activated this region, the activation was more widespread in the word task, thus mirroring the current reading results. Similarly, Wise *et al.* (1991) found bilateral temporal activation in a task involving judgements of super/subordinate relationships among spoken-word pairs. In that study however, a passive nonword listening task activated these regions equivalently, prompting the authors to suggest that semantic and phonological networks may be highly overlapping at these sites. By contrast, Petersen *et al.* (1989) using a task that involved generating a verb to a related target noun and contrasting this with a simple noun repetition baseline task, observed pre-frontal activation but no temporal activation. However, Shaywitz *et al.* (1995a) reasoned that verb generation may make only minimal semantic demands (the task can be accomplished simply by strong lexical associations) and therefore induced subjects to generate sets of exemplars for a given category label. This task produced temporal activation of greater magnitude than that produced by a rhyme generation control, again suggesting a semantic role for this region. Finally, lesion studies and data from aphasia have suggested that damage to temporal and temporoparietal sites often results in semantic deficits (Hart and Gordon, 1990).

The key finding of the present study was a reliable increase in activation in both hemispheres at temporal sites for



semantic category judgements over rhyme judgements when printed stimuli were used. This result is consistent with the conclusions of Wise *et al.* (1991) and Demonet *et al.* (1992) suggesting a semantic role for the temporal lobe. By obtaining this result with a novel set of tasks, with behaviourally similar control conditions and, most notably, with visually presented stimuli, we have effectively ruled out the complication in those two studies where the activation of the temporal lobe was obtained with spoken word stimuli, which should activate the superior temporal gyrus as a matter of course. Moreover, in the present experiment the convergence of results using different baseline tasks (line and case), coupled with the fact that other regions showed very different patterns of activation, strengthens the conclusion that lexical-semantic processing makes specific demands on both the middle and superior temporal gyri. However, this region appears to function differently in males and females, the finding to which we now turn.

### Sex differences

Two distinct and robust sex differences were observed in this experiment. Moreover, these differences appear to be independent (i.e. there were no higher order interactions involving both). First, in the total area analyses as well as in three separate regions (medial extrastriate, middle and superior temporal gyri) we observed that the rhyme-line subtraction produced less widespread activation than the semantic category-line one in males. This finding lends itself to the interpretation that networks engaged by phonological and lexical-semantic processing are, to some extent, spatially distinctive for males. In females rhyme-line subtractions produced activation levels similar to those in males but at no site examined was there an increase in activation in the semantic category-line subtraction. This sex difference was also apparent in the converging subtractions (e.g. rhyme-case versus semantic category-case). A straightforward though tentative interpretation of the failure to find an increase from rhyme-line to semantic category-line is that the phonological and semantic networks overlap more in women than in men. This interpretation is consistent with the general conclusion, based on lesion studies, that language relevant regions are more circumscribed in females than in males (Kimura, 1987, 1992).

The second relevant sex difference, previously reported in abbreviated form in Shaywitz *et al.* (1995b), involved differences between hemispheres. We observed most strongly in the inferior frontal gyrus, but also in the total area scanned analyses, equivalent LH and RH activation in females. In males activation was greater in the LH. These differences cannot be attributed simply to differences in the overall activation levels; no main effects of sex were obtained in any of the analyses.

Hemispheric differences of this kind have been suggested in a number of behavioural studies (McGlone, 1980; Lukatela *et al.*, 1986; Crossman and Polich, 1988; Luh and Levy,

1995; Zaidel *et al.*, 1995). For example, Lukatela *et al.* (1986) presented data from a lateralized lexical decision task with speakers of the Serbo-Croatian language. The writing system in this language has been transcribed in two distinct scripts. Latencies and accuracy on words and pseudowords that were either alphabetically and phonologically ambiguous (pronounced differently in the Roman and Cyrillic scripts) or phonologically unambiguous (possessing a unique pronunciation in both scripts) were measured. For words, phonological ambiguity effects (relative slowing on phonologically ambiguous targets) were equivalent for males and females in the right visual field (i.e. LH) but stronger in females in the left visual field (i.e. RH). The investigators concluded that the increased sensitivity on a phonological variable in the RH of females probably reflects greater phonological representation in that hemisphere. Luh and Levy (1995) presented subjects with tachistoscopically displayed CVC (consonant, vowel, consonant) displays presented to both the left visual field (RH) and right visual field (LH). Subjects were required to pronounce the stimulus display. Overall, a LH advantage was obtained. However, in two separate experiments females showed much smaller LH advantages than males. Thus, in a study that measured basic decoding associated with each hemisphere, the evidence suggested greater RH phonological representation for females relative to males and this is consistent with the findings from the study of Lukatela *et al.* (1986). The results of the present study also suggest greater LH dominance in phonological regions for males than for females. With cortical activation patterns the present study provides a more direct source of evidence for hemispheric differences than behavioural studies can.

Both of these types of cerebral difference between the sexes, differences with respect to localization of phonological and semantic function and differences in hemispheric lateralization, require further investigation. Whether they truly reflect biological constraints on brain organization for reading or, alternatively, whether they reflect educational or strategic variability must be considered in further studies. However, it is apparent that in future investigations of language function male/female differences, whether behavioural or metabolic, must be considered a relevant variable.

The results from the present experiment allow us to sketch a possible architecture for some of the anatomical sites associated with the component processes in reading. Initial visual processing must make demands on striate and extrastriate occipital sites. Mapping this featural information onto orthographic representations seems to engage first lateral and then medial extrastriate networks. (Given the evidence that nonword letter strings and real words activated lateral sites equally while real words made greater demands on medial sites than either consonant strings or pronounceable nonwords, it might be speculated that the flow of information passes from lateral to medial sites.) From this point, assembling a phonological representation engages a



number of sites within the inferior frontal gyrus and temporal lobe, with inferior frontal sites more LH dominant in males but highly bilateral in females. Access to, and decisions about, lexical-semantic information engages the middle and superior temporal gyri in both hemispheres, with the possibility of greater overlap within these regions between phonological and lexical-semantic networks for females than for males.

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