Functional MRI of phonological and semantic processing in temporal lobe epilepsy

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Summary
Phonological and semantic aspects of language were examined in patients with unilateral temporal lobe epilepsy (TLE) and healthy controls using functional MRI. We expected to replicate previous findings in healthy individuals showing relatively greater activation in frontal regions for phonological compared with semantic processing, and greater activation in temporal regions for semantic compared with phonological processing. We hypothesized that differences between patients with left TLE and healthy controls would be found in the pattern of left temporal cortical activation associated specifically with semantic processing. We examined how phonological and semantic components of language may be differentially represented in patients with unilateral temporal epileptogenic foci compared with matched controls.

Introduction
Several investigators have demonstrated the clinical utility of functional MRI (fMRI) in determining language dominance in preoperative patients with epilepsy (Binder et al., 1996b; Hertz-Pannier et al., 1997; Stapleton et al., 1997; Benson et al., 1999). The verb generation task, in which a participant thinks of a verb in response to seeing or hearing a noun, has been used to determine language dominance in fMRI and has provided concordant evidence with the Wada test (Worthington et al., 1997; Benson et al., 1999). Although the verb generation task appears to be robust in identifying language relevant areas, specifically in inferior frontal cortex, the minimal cognitive processes engaged by the typical baseline fixation task (e.g. viewing a cross-hair or hearing a tone) prevent analysis of separate linguistic components. The blood oxygen level dependent (BOLD) response during verb generation represents phonological and semantic aspects of expressive language, as the individual is required to generate in his or her mind the sound of a verb that is semantically related to a noun. Similarly, the semantic decision task used by Springer and colleagues (Springer et al., 1999) to study language lateralization in patients with temporal lobe epilepsy (TLE) engages both phonological and semantic processes in comparison with their control task (tone monitoring). We examined how phonological and semantic components of language may be differentially represented in patients with unilateral temporal epileptogenic foci compared with matched controls.

Intracarotid sodium amytal studies of patients with TLE...
who have left lateralized language have suggested that both phonological and semantic processing are interrupted following left hemisphere injection, regardless of side of seizure focus (Fedio et al., 1997; Ravdin et al., 1997). However, sodium amytal injections affect a wide area of cortex, so differential organization within the dominant hemisphere cannot be addressed with this technique. Tasks such as naming and verbal fluency have been shown to reveal subtle semantic processing impairments in patients with left TLE (Saykin et al., 1995; Troster et al., 1995). A previous fMRI study of TLE patients suggested that impaired naming ability may be associated with diminished blood flow to temporal cortex (Henry et al., 1998). Ours is the first nearoimaging study reported to date, however, to examine semantic and phonological processes and their potential differences in inter- or intra-hemispheric organization in patients with TLE.

To isolate phonological and semantic processing, we adopted tasks employed by Shaywitz et al. (1995) and Pugh et al. (1996). This group used a hierarchical subtraction technique to isolate orthographic, phonological and semantic processing components of reading in healthy volunteers. Pugh and colleagues found that the phonological and semantic processing requirements of rhyme- and category-decision tasks activated different cortical regions (Pugh et al., 1996). Inferior and lateral orbital frontal regions were found to be more active in subtractions isolating phonological compared with semantic processing. Superior and middle temporal regions, in contrast, were more active for subtractions isolating semantic processing than for other subtractions. We expected to replicate Pugh and colleagues’ findings in healthy individuals and we hypothesized that in patients with left TLE, a differential linguistic representation would be most likely found for processes subserved by the regions of the brain affected by the seizure focus. Therefore, given a probable loss of functional neurones in left temporal cortex, we expected that patients with TLE in the dominant hemisphere would show decreases in left temporal activation for semantic relative to phonological components of language tasks compared with healthy control participants. Although both left temporal and inferior frontal regions have been implicated in semantic processing (Demb et al., 1995; Vandenberghe et al., 1996; Gabrieli et al., 1998; Poldrack et al., 1999), we expected that the processing requirements of the particular semantic decision task used here might reveal differences between patients with left TLE and controls specifically in left temporal cortex. We did not predict differences between the right TLE group and controls, but included these patients as a seizure control group. Language dominance had previously been determined to be in the left hemisphere for all of the epilepsy patients.

Sex differences in cerebral organization of semantic and phonological processes were also examined. Pugh et al. (1996) found that females exhibited greater bilateral activation in frontal regions than males for phonological and semantic analyses. Other neuroimaging studies, however, have failed to find reliable sex differences in linguistic processing in healthy individuals (Buckner et al., 1995; Price et al., 1996; Frost et al., 1999). Therefore, potential sex differences in the patient and control groups on tasks similar to those used by Pugh et al. (1996) were of specific interest.

Methods
Participants
Twenty-one individuals with pharmacologically intractable TLE (10 with left and 11 with right temporal foci) and 11 controls participated. In each case the temporal lobe onset of seizures was confirmed by scalp EEG recordings. Seizure and neuropsychological characteristics of the patients are shown in Table 1. There were five men and five women in the left TLE group, and six men and five women in the right TLE group. There were no significant differences between the left and right TLE groups in terms of seizure frequency, age of first seizure onset, or verbal IQ. Preoperative structural MRI scans revealed the presence of mesial temporal sclerosis (MTS) in five participants with left TLE and six participants with right TLE. Four cases (two left, two right) had evidence of focal neocortical abnormalities (tumour, dysplasia or previous corticectomy); in all other cases scalp electrographic findings were compatible with a mesial temporal localization. Individuals with multiple lesions or non-focal epileptogenic events were excluded. Language lateralization was found to be in the left hemisphere in all patients, based on the sodium amytal test.

The control group comprised six men and five women who were recruited from local hospital and university communities. The control group did not differ significantly from the patient groups in age (see Table 1), but they had attained a slightly higher mean level of education (16.8 years versus 13.9 and 14.2 years in the left and right temporal groups, respectively). Control participants were all right-handed. All experimental procedures were approved by the Institutional Review Board of the Toronto Western Hospital and informed consent was obtained from all participants.

Behavioural tasks and procedure
Participants completed three types of tasks while being scanned. Each task required participants to make same/different decisions about pairs of orthographic stimuli. The first task, an orthographic decision, required participants to determine whether the alternating cases of two strings of letters matched (e.g. AEaE and AeaE); the second task, a phonological decision, required participants to determine whether two nonsense words rhymed (e.g. klage and maige); and the third task, a semantic decision, required participants to determine whether two words belonged to the same category (e.g. pansy and rose). Comparison of the rhyme and case tasks was intended to isolate regions associated with phonological processing. Comparison of the category and case tasks was used to identify regions associated with both
Table 1 Participant characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age at testing (years)</th>
<th>Handedness</th>
<th>Education (years)</th>
<th>Age of seizure onset (years)</th>
<th>Seizure frequency per month*</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left TLE</td>
<td>35.2 (19.6–56.0)</td>
<td>8 2</td>
<td>13.9 (12–16)</td>
<td>11.7 (0.50–28.0)</td>
<td>18.7 (2–105)</td>
<td>93.2 (70–123)</td>
<td>89.1 (80–100)</td>
</tr>
<tr>
<td>Right TLE</td>
<td>34.0 (18.4–55.5)</td>
<td>10 1</td>
<td>14.2 (12–19)</td>
<td>12.5 (0.75–37.0)</td>
<td>15.5 (1–45)</td>
<td>90.9 (69–118)</td>
<td>95.1 (62–119)</td>
</tr>
<tr>
<td>Control</td>
<td>34.2 (22.5–58.2)</td>
<td>11 0</td>
<td>16.8 (13–21)</td>
<td>NA</td>
<td>NA</td>
<td>Not assessed</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

NA = not applicable; TLE = temporal lobe epilepsy. *Seizure frequency per month is based on number of seizures in the 6 months prior to testing.

phonological and semantic processing. The category versus rhyme comparison indicated activity specific to semantic processing.

The decision tasks were presented to participants by way of a projector onto a translucent screen that was placed at their feet. Participants viewed the stimuli through a mirror above their head. Movement during the scan was minimized with padding. All participants received a practice run of the test while they lay in the scanner prior to any images being taken. Four stimulus pairs from each type of task were presented during the practice. These stimuli were not used again during the task, nor were any stimuli repeated during the actual test. Fifty stimulus pairs were presented for each type of task during the functional scan. Similar to the method of Pugh et al. (1996), a block paradigm was employed, with five blocks of each decision type (32 s per block) appearing in the following order: case, rhyme, category. There were no rest periods between blocks. Participants pressed a mouse button with their left hand to indicate a positive match. No feedback was given during the performance of the task.

**Image acquisition**

Imaging was performed on a 1.5 T Signa ‘Echospeed’ MRI system (GE Medical Systems, Milwaukee, Wisc., USA). Following a sagittal localizing scan, 2D anatomical images were obtained. Eight axial slices (7 mm thick with a 1 mm gap; in-plane resolution 2.4×2.4 mm) were acquired, with the first slice aligned 4 mm below the bicommissural plane (Talairach and Tournoux, 1988). Functional images were subsequently acquired with the same slice prescription using a spiral trajectory through k-space (four shot; echo time, TE = 40 ms; repetition time, TR = 640 ms; flip angle = 62°, 2.56 s/frame).

**Image analysis**

Functional images were corrected for motion (Woods et al., 1996) and baseline correction was performed using a high-pass temporal filter. Images corresponding to the first 5.12 s of task performance were discarded to account for the haemodynamic response delay. The time course of the fMRI data at each pixel was correlated with the appropriate square-wave contrast functions for each of the three block comparisons (rhyme versus case, semantic versus rhyme, and semantic versus case) using the Stimulate software package (Strupp, 1996). Each resultant correlation (r) map was thresholded for each participant at 2.25 SD beyond the mean of the overall distribution of r-values within the brain (one-sided, P < 0.01), with a cluster size of two contiguous pixels. This method of thresholding attempts to keep the empirically derived false-positive detection rate constant with a threshold that is based on an estimate of the background distribution of r-values for each scan.

Given the considerable variability in pathology in TLE (Armstrong, 1993) and heterogeneity of language representation in the brains of individuals with TLE (Ojemann et al., 1989), the functional data were not averaged across individual brains (see also Woods, 1996). Rather, region of interest analyses were performed for each individual, using the bicommissural landmark and the Talairach and Tournoux brain atlas (Talairach and Tournoux, 1988). Regions of interest (and corresponding Brodmann areas) included those examined by Pugh et al. (1996): inferior frontal (44, 45), orbital frontal (47, 10), prefrontal dorsolateral (46), middle temporal (21, 37, 39), superior temporal (22, 42), lateral extrastriate (18, 19, 7) and medial extrastriate (18, 7). Given the greater number of slices obtained in the present study compared with Pugh and colleagues’ study, other regions were also analysed for task and group differences, including insula, middle and superior frontal gyri (8, 9), inferior parietal (40), and anterior (32, 23, 24) and posterior cingulate gyrus (30, 31, 23). Dependent measures analysed by region were spatial extent of activation (number of pixels) and per cent signal difference between the mean BOLD signal during task blocks compared with the mean signal during control blocks. Although spatial extent of activation, rather than per cent signal difference, is typically analysed in fMRI studies of language representation, we examined whether there was in fact convergence between the two measures.

**Results**

**Behavioural results**

Figure 1 shows the number of correct responses by task type for each group. A three (task type) by three (group) analysis
of variance with repeated measures on the first factor was performed for correct responses and reaction time. Significant main effects of task type \([F(2,56) = 6.97, P < 0.01]\) and group \([F(2,28) = 4.10, P < 0.05]\) were found for the accuracy measure. Post hoc tests revealed that participants gave a greater number of correct responses under the category decision compared with the case decision task, but no significant differences were found for the rhyme decision task. Accuracy was higher for the control group in comparison with the right TLE group, but no significant differences were found between the left TLE group and either the control or right TLE group.

Figure 2 shows reaction time scores by task type and group. Main effects of task type \([F(2,56) = 41.75, P < 0.001]\) and group \([F(2,28) = 11.46, P < 0.001]\) were found. Reaction times were significantly faster for the category decision task compared with the rhyme decision and case decision tasks. Reaction times for the rhyme decision task were also faster than for the case decision task. Post hoc tests of group differences showed that both the left and right TLE groups responded more slowly compared with the control group. There were no significant group \(\times\) task-type interactions for either accuracy or reaction time measures.

**Functional results**

Mean pixel counts and per cent signal differences by group and region of interest across processing type are presented in Table 2. Prior to analysing each region of interest, hemispheric differences in overall activation were assessed. A main effect of hemisphere was observed for spatial extent of activation \([F(1,29) = 17.77, P < 0.001]\), with greater left compared with right hemisphere activity appearing for all groups across each processing type subtraction. No differences by hemisphere were found for per cent signal intensity. Differences in spatial extent of activation by processing type were observed, however, within each hemisphere. Overall, greater activity was found in the left hemisphere for task subtractions involving phonological processing (rhyme minus case decision and category minus case decision) compared with semantic processing alone (category minus rhyme decision) \([F(2,58) = 8.50, P < 0.001]\). A greater spatial extent of activation was also observed in the right hemisphere for the combined phonological and semantic processing condition (category minus case decision) compared with either phonological or semantic processing alone \([F(2,58) = 3.39, P < 0.05]\).

**Frontal lobes**

In left lateral orbital frontal regions, both spatial extent \([F(2,58) = 4.30, P < 0.02]\) and mean signal intensity \([F(2,58) = 4.79, P < 0.02]\) were greater for the combined phonological and semantic processing condition than for semantic processing alone. The same pattern was observed for spatial extent in left superior frontal gyrus \([F(2,58) = 8.35, P < 0.001]\).

Left inferior frontal regions also demonstrated greater activation under both subtractions involving phonological processing compared with semantic processing alone \([F(2,58) = 9.39, P < 0.001]\) and \([F(2,58) = 8.01, P < 0.001]\), for spatial extent and signal difference, respectively. Figure 3 illustrates a representative example of this pattern of activation in a 30-year-old control participant. However, there was a significant interaction of processing type by group for the spatial extent measure \([F(4,58) = 2.92, P < 0.03]\), indicating that this pattern was present only in control subjects. The left temporal group showed no differences by processing type, whereas the right temporal group showed greater activation only for the combined semantic and phonological condition compared with the semantic subtraction alone. Of interest, a main effect of group was found in left inferior frontal cortex for per cent signal difference \([F(2,58) = 4.92, P < 0.02]\). The left and right temporal groups both showed a higher signal increase in left inferior frontal cortex compared with controls across all processing types.

A trend toward a main effect of group for spatial extent of activation was also observed in left dorsolateral prefrontal cortex \([F(2,29) = 3.06, P = 0.06]\). Post hoc contrasts revealed a significantly greater spatial extent of activation for left TLE patients compared with controls across processing types \([F(1,19) = 7.10, P < 0.02]\). Figure 4 illustrates this difference in prefrontal dorsolateral activation for a patient.
with left TLE compared with an age- and sex-matched control participant.

**Temporal lobes**

A greater spatial extent of activation was found in left superior temporal gyrus for phonological compared with semantic processing alone \( [F(2,58) = 4.79, P < 0.02] \). However, this main effect was qualified by a group \( \times \) processing type interaction \( [F(4,58) = 2.74, P < 0.04] \), which revealed that this pattern was present only in the control group. No significant differences in left superior temporal activation were observed between processing types for the left or right TLE groups. Analysis of signal intensity differences revealed a similar group \( \times \) processing type interaction in this region \( [F(4,58) = 4.63, P < 0.01] \). In left middle temporal gyrus, there was a trend toward a main effect of processing type \( [F(2,58) = 2.43, P < 0.10] \). This trend reflected a greater spatial extent for phonological and semantic processing combined than for phonological processing alone. There were no main effects or interactions involving group for this region.

Analysis of right superior temporal gyrus revealed a main effect of group \( [F(2,29) = 3.57, P < 0.05] \). The right TLE group showed a significantly smaller spatial extent of activation compared with the control group across processing types. Figure 5 illustrates this effect in a patient with right TLE compared with an age- and sex-matched control participant. In contrast, a trend toward a higher per cent signal difference was found in right middle temporal gyrus for left TLE patients compared with controls across processing types \( [F(2,29) = 2.89, P < 0.08] \). A significant interaction for per cent signal difference was also found \( [F(4,58) = 3.35, P < 0.05] \).

### Table 2
Mean spatial extent of activation and signal intensity change (SE) by group and region across processing type

<table>
<thead>
<tr>
<th>Region of interest (Brodmann area)</th>
<th>Group</th>
<th>Control</th>
<th>Left TLE</th>
<th>Right TLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pixel count (SE)</td>
<td>Signal change (SE)</td>
<td>Pixel count (SE)</td>
<td>Signal change (SE)</td>
</tr>
<tr>
<td>Inferior frontal (44/45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>6.0 (3.1)</td>
<td>0.9 (0.3)</td>
<td>5.5 (2.5)</td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td>Right</td>
<td>2.2 (1.3)</td>
<td>0.8 (0.3)</td>
<td>4.9 (2.0)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>Prefrontal dorsolateral (46)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Left</td>
<td>1.0 (0.6)</td>
<td>0.5 (0.2)</td>
<td>3.3 (1.8)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>Right</td>
<td>0.8 (0.4)</td>
<td>0.5 (0.2)</td>
<td>3.0 (1.6)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>Lateral orbital (47/10)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>16.7 (5.1)</td>
<td>1.6 (0.2)</td>
<td>8.7 (4.4)</td>
<td>1.7 (0.5)</td>
</tr>
<tr>
<td>Right</td>
<td>13.3 (4.2)</td>
<td>1.6 (0.2)</td>
<td>6.8 (2.8)</td>
<td>1.7 (0.5)</td>
</tr>
<tr>
<td>Superior and middle frontal gyri (8/9)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Left</td>
<td>7.7 (3.3)</td>
<td>0.8 (0.2)</td>
<td>7.8 (3.5)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>Right</td>
<td>4.8 (2.4)</td>
<td>0.6 (0.2)</td>
<td>7.4 (2.9)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Superior temporal (22/42)</td>
<td></td>
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<tr>
<td>Left</td>
<td>5.2 (1.8)</td>
<td>1.2 (0.2)</td>
<td>4.7 (2.0)</td>
<td>1.5 (0.4)</td>
</tr>
<tr>
<td>Right</td>
<td>4.3 (1.4)</td>
<td>1.0 (0.2)</td>
<td>3.3 (1.6)</td>
<td>1.3 (0.5)</td>
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<tr>
<td>Middle temporal (21/37/39)</td>
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<tr>
<td>Left</td>
<td>7.0 (2.0)</td>
<td>1.2 (0.2)</td>
<td>4.4 (1.6)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Right</td>
<td>2.9 (1.1)</td>
<td>1.0 (0.2)</td>
<td>2.8 (1.0)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
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</tr>
<tr>
<td>Left</td>
<td>1.0 (0.4)</td>
<td>0.4 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>Right</td>
<td>2.2 (1.8)</td>
<td>0.5 (0.5)</td>
<td>1.7 (1.1)</td>
<td>0.6 (0.4)</td>
</tr>
<tr>
<td>Lateral extrastriate (18/19/7)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>5.6 (2.1)</td>
<td>1.1 (0.3)</td>
<td>4.7 (2.1)</td>
<td>1.4 (0.5)</td>
</tr>
<tr>
<td>Right</td>
<td>4.2 (1.7)</td>
<td>1.1 (0.3)</td>
<td>1.8 (0.8)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>Medial extrastriate (18/7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4.1 (2.2)</td>
<td>1.0 (0.2)</td>
<td>3.5 (1.1)</td>
<td>1.8 (0.4)</td>
</tr>
<tr>
<td>Right</td>
<td>2.4 (0.8)</td>
<td>1.0 (0.3)</td>
<td>2.4 (0.9)</td>
<td>1.2 (0.4)</td>
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<tr>
<td>Inferior parietal (40)</td>
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</tr>
<tr>
<td>Left</td>
<td>7.1 (2.1)</td>
<td>1.2 (0.2)</td>
<td>3.0 (1.2)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>Right</td>
<td>3.4 (1.3)</td>
<td>0.8 (0.2)</td>
<td>3.1 (1.0)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Anterior cingulate (32/23/24)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Left</td>
<td>3.2 (1.6)</td>
<td>0.9 (0.2)</td>
<td>0.6 (0.8)</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>Right</td>
<td>2.0 (1.91)</td>
<td>0.8 (0.3)</td>
<td>1.0 (0.5)</td>
<td>0.7 (0.3)</td>
</tr>
<tr>
<td>Posterior cingulate (30/31/23)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.9 (0.6)</td>
<td>0.3 (0.2)</td>
<td>0.6 (0.8)</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>Right</td>
<td>0.4 (0.3)</td>
<td>0.2 (0.2)</td>
<td>0.6 (0.5)</td>
<td>0.3 (0.2)</td>
</tr>
</tbody>
</table>
showing a greater signal change for the left TLE group compared with controls in right middle temporal gyrus specifically under the phonological processing condition.

Other regions
In the right insula, a main effect of processing type was observed [$F(2, 58) = 3.50, P < 0.04$], such that the phonological and semantic processing combined condition...
Sex differences

Overall, males and females in both the patient and control groups performed similarly. A few main effects of sex, however, were found. Males showed a greater spatial extent in left middle temporal gyrus compared with females under the phonological processing condition \(F(1,26) = 6.85, P < 0.02\). Females showed a greater spatial extent of activation in the left hemisphere than males in the semantic processing condition \(F(1,26) = 6.85, P < 0.02\), a difference that was most prominent in lateral orbital and dorsolateral prefrontal cortex \(F(1,26) = 4.28, P < 0.05,\) and \(F(1,26) = 4.25, P < 0.05,\) for the respective regions. This pattern was also observed for the signal intensity measure \(F(1,26) = 9.91, P < 0.01,\) and \(F(1,26) = 4.47, P < 0.05,\) for lateral orbital and dorsolateral prefrontal cortex, respectively. Finally, spatial extent was greater in right inferior frontal cortex in females compared with males under the semantic processing condition \(F(1,26) = 8.06, P < 0.01\).

Age of onset and seizure frequency

No significant correlations were found between regional activation (spatial extent of activation or per cent signal difference) and either age of first seizure onset or seizure frequency.

Discussion

Consistent with the findings of Pugh and colleagues’ (1996) study of healthy adults, we found greater activity in left lateral orbital and inferior frontal cortex under subtractions involving phonological processing compared with semantic processing alone. This finding was qualified by an interaction with group for spatial extent of activation. Patients with left TLE failed to show a difference by processing condition in left inferior frontal cortex, while the right TLE group showed a greater spatial extent under the combined phonological and semantic condition compared with the semantic condition alone. However, we failed to replicate Pugh et al.’s (1996) findings of greater activation in temporal cortex for semantic processing. Neither patients nor controls showed greater activation in left superior or middle temporal gyri during semantic compared with phonological processing. In fact, the control group showed an increased spatial extent of activation in left superior temporal gyrus under the phonological compared with the semantic processing condition, while neither patient group showed differences by task type in this region. Only a trend was observed across groups in middle temporal gyrus toward greater spatial extent of activation during both phonological and semantic processing compared with phonological processing alone. The difference between our results and Pugh and colleagues’ findings may be a function of power, as they had slightly more participants and longer scanning time; we note that it is not related to differential coverage of the temporal lobe in our respective slice prescriptions. We also note that other studies have emphasized the role of temporal cortex, particularly superior temporal gyrus, in phonological processing (Demonet et al., 1992; Zatorre et al., 1992; Binder et al., 1996; Rumsey et al., 1997). Furthermore, neither our nor Pugh and colleagues’ study imaged more inferior temporal regions [Brodmann area (BA) 20, 38] that have been identified as being involved in semantic analysis (Vandenbergh et al., 1996; Devlin et al., 2000; Zahn et al., 2000).

We had predicted that patients with left TLE would show differences in activation patterns, particularly with respect to left temporal lobe activation for semantic processing. Contrary to expectation, however, they demonstrated no differences from controls or patients with right TLE in either spatial extent or signal intensity in this region for phonological or semantic conditions. Nonetheless, this group did demonstrate some differences in activation patterns in other regions when compared with controls. First, they showed a higher per cent signal change in right middle temporal gyrus, specifically during phonological processing. In addition, they showed a greater spatial extent of activation in left prefrontal dorsolateral cortex across processing types. Finally, a higher per cent signal change was found in left inferior frontal cortex for patients with left TLE compared with controls. This latter finding was also observed in patients with right TLE. However, activation patterns for this group were largely similar to those observed in controls except for a smaller regional activation across processing type in the right superior temporal lobe.

The differences found between the participants with left TLE and controls in left frontal cortex might be accounted for by the greater difficulty of the task for the patients compared with controls. Although changes in anterior cingulate, not dorsolateral prefrontal, activation have been most closely associated with increases in task difficulty (Barch et al., 1997; Paus et al., 1998), increased prefrontal activation has been observed under conditions of increasing task difficulty (Baker et al., 1996). However, analysis of accuracy on these tasks only revealed a difference between the right TLE and control groups in terms of the number of errors made. Although both patient groups responded more slowly than controls across decision types, which is consistent with early studies showing that reaction times were longer for adults with cerebral damage compared with controls (Benton and Joynt, 1959; De Renzi and Faglioni, 1965; Howes and Boller, 1975), the left TLE group was no less accurate than controls. Between-group differences in task difficulty, therefore, do not appear to account for the differences between the left TLE and control groups in
spatial extent of activation and signal change found in left
dorsolateral prefrontal and inferior frontal cortex, respectively.

A study by Shaywitz and colleagues of semantic and
phonological processing in individuals with dyslexia
suggested that posterior left temporal pathology may be
associated with increased activation in left frontal cortex
during phonological processing (Shaywitz et al., 1998). They
found both increased left frontal activation and decreased
posterior left temporal activation in participants with dyslexia.
Similar results were reported by Brunswick and colleagues
using PET when adult dyslexics were required to read aloud
(Brunswick et al., 1999). Although we did not observe
differences in left temporal cortex in our left TLE patients,
we did find increased activation in left prefrontal dorsolateral,
left inferior frontal, and right middle temporal regions in
these patients. In conjunction with the findings of Shaywitz
et al. (1998) and Brunswick et al. (1999), our results suggest
that increased left frontal activity is likely to be observed
during linguistic processing in the presence of left temporal
abnormality.

Contrary to our expectation, the presence of a left temporal
epileptogenic focus did not selectively affect either accuracy
on the semantic decision task or the magnitude or spatial
extent of activation in this region. There are several possible
explanations for this negative finding. First, the decision task
may not be sufficiently sensitive to reveal processing deficits.
We note that while tasks such as naming and verbal fluency
have been shown to reveal subtle semantic processing
impairments in patients with left TLE (Saykin et al., 1995;
Troster et al., 1995), we know of no relevant behavioural
data regarding similar impairments on semantic decision
tasks such as the one used here. Thus, while left temporal
regions may participate in this task, they may not be crucial
for adequate performance. Secondly, we might speculate that
the increased activation seen in left TLE patients in frontal
regions reflects a functional strategy difference that serves
to support accurate task performance. This is similar to the
arguments Shaywitz et al. (1998) offered regarding their
findings in dyslexic patients. Finally, given that many of our
left TLE patients had seizure foci in mesial temporal
structures, it is possible that there was little impact of seizures
on the organization of language areas in middle and superior
temporal neocortex. Whether activity during semantic
processing is more likely to be altered in inferior temporal
regions in TLE should be a topic of future investigations,
particularly in light of recent advances in controlling for
susceptibility artefacts associated with functional imaging
of these areas (Devlin et al., 2000). Studies of language
lateralization in TLE, using intracarotid sodium amytal or
fMRI techniques, suggest that functional re-organization
(toward a pattern of greater right hemisphere contribution)
is strongly associated with age of onset of seizures (Satz
et al., 1988; Springer et al., 1999). We did not find any such
correlations in our data, although this may be a consequence
of the relatively small sample size.

In contrast to the multiple and consistent sex differences
reported by Shaywitz et al. (1995) and Pugh et al. (1996) in
healthy individuals who performed tasks similar to those
used here, neither patients nor healthy controls showed
reliable sex differences in activation. Females showed greater
right inferior frontal activation during semantic processing
than males, which is consistent with the findings of Pugh
et al. (1996) and Shaywitz et al. (1995), but females also
showed greater left hemisphere activation, specifically in
frontal regions, compared with males during semantic
processing. Although Pugh and colleagues’ findings of sex
differences are consistent with several behavioural and lesion
studies (McGlone, 1977, 1978; Lukatela et al., 1986;
Kimura, 1987, 1992; Crossman and Polich, 1988; Zaidel
et al., 1995), other neuroimaging studies have failed to find
reliable sex differences in linguistic processing (Buckner
et al., 1995; Price et al., 1996). Frost and colleagues recently
reported similar patterns of regional activation in a large
group (n = 100) of healthy men and women using fMRI
and a semantic monitoring task (Frost et al., 1999). The
inconsistency in the neuroimaging literature regarding sex
differences in healthy volunteers may be, in part, a reflection
of the different cognitive paradigms used to elicit linguistic
responses. Nonetheless, using the same type of paradigm as
Pugh et al. (1996), we found few reliable sex differences,
consistent with the findings of Frost et al. (1999).

The results reported here suggest that increases in left
frontal cortical activity, as well as an increased signal change
in right middle temporal gyrus, are likely to be observed
in patients with left TLE during linguistic processing. These
results converge with a study of dyslexic patients by showing
increased left frontal activity in the presence of left temporal
dysfunction. Surprisingly, patients with right TLE, but not
left TLE, in this study showed poorer performance on the
linguistic tasks compared with controls, as well as an
associated decrease in right superior temporal activation.
We are unable to account for the accuracy difference, but note
that other studies have reported atypical lateralization of
language in patients with right TLE (Helmstaedter et al.,
1997). Nonetheless, the lack of a behavioural deficit in our
left TLE group permits stronger conclusions about the activity
in brain regions subserving normal task performance. In
summary, our results indicate a greater participation of regions
outside the left temporal lobe in left TLE patients, suggesting
possible inter- and intra-hemispheric functional reorganiza-
tion of language representation.

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