Human brain language processing areas identified by functional magnetic resonance imaging using a lexical decision task

Giovanna Calandra-Buonaura
Gianpaolo Basso
Maria Luisa Gorno-Tempini
Marco Serafini*
Giuseppe Pagnoni**
Patrizia Baraldi**
Carlo Alberto Porro***
Paolo Nichelli

Department of Neurosciences, University of Modena and Reggio Emilia
*City of Modena Local Health Authority
**Department of Biomedical Sciences, University of Modena and Reggio Emilia
***Department of Biomedical Sciences, University of Udine, Italy

Reprint requests to: Prof. Paolo F. Nichelli, Dipartimento di Neuroscienze, Università di Modena e Reggio Emilia, Via del Pozzo, 71, 41100 Modena, Italy. E-mail: nichelli@unimo.it

Accepted for publication: July 30, 2002

Summary

The purpose of this study was to validate a functional magnetic resonance imaging (fMRI) paradigm to activate both anterior and posterior language areas while collecting accuracy and reaction time data on subjects’ performance. The paradigm was based on alternating graphemic and lexical decision tasks. In line with the classical model of language organisation, based on lesion data, and with the results of previous neuroimaging studies, cortical activation associated with lexical decision-making was strongly lateralised to the left hemisphere and involved a network of regions in the frontal, temporal and parietal lobes. Single subject analysis demonstrated that the activation paradigm we propose is suitable for detecting language processing areas in humans for clinical studies.

KEY WORDS: Functional magnetic resonance, graphemic decision, language mapping, lexical decision.

Introduction

 Patients with brain tumours, arterovenous malformations and intractable epilepsy, who are considered for surgical treatment in the left hemisphere, often need invasive testing to avoid resecting cortical language areas. Both the Wada test (which involves intracarotid injection of sodium amytal) and recording with subdural and depth electrodes are used for this purpose (1). Positron emission tomography (PET) can also be used (2) to demonstrate areas activated by various language-related tasks. However, PET is a rather expensive method, it is not widely available, and it is still minimally invasive. More recently, functional magnetic resonance imaging (fMRI) has been proposed as a non-invasive alternative for mapping cognitive functions. Several authors (3-10) have used fMRI in conjunction with language tasks with the aim of mapping regions of the brain that the surgeon should avoid resecting. However, wider application of this technique in the clinical setting is prevented by the fact that language production cannot be tested during scanning because it generates motion artefacts. Various alternatives have been proposed: subvocal phonemic fluency (i.e., the generation of letters beginning with a target input letter), semantic fluency (i.e., the generation of words belonging to an input category), and silent verb generation (5,6,9,11). Yet, these tasks do not allow the monitoring of patients’ performance during scanning, which is crucial in order to identify a lack of activation in candidate language processing areas. Furthermore, recent studies have demonstrated that areas that are commonly associated with language production can also be associated with phonological and lexical processing (12,13).

Based on this evidence, we devised a testing paradigm for use in clinical settings to identify language processing areas while monitoring patients’ performance. Since the paradigm was intended for use with brain-damaged patients, tasks were required that were simple enough to be performed with few errors, even without training. The paradigm involved comparing brain activation associated with lexical and with graphemic decision tasks. In the former, the subjects were not required to analyse the words semantically. However, since participants may engage in covert or incidental analysis of word meaning, areas that are activated by semantic processing could also be found. Previous studies (11,12) have demonstrated that both tasks involving phonological processing and those in-

Functional Neurology 2002; 17(4): 183-191
volving semantic processing activate left prefrontal areas corresponding to BA 44 and 45 (including Broca’s area). It has also been demonstrated that this activation is strongly related to language dominance, assessed by the Wada test (16).

The purpose of this study was therefore to validate in a group of normal subjects a testing paradigm that was simple enough to be applied in a clinical setting, and that could reliably activate both the anterior and the posterior areas involved in language processing.

Materials and methods

Subjects

Ten healthy right-handed volunteers (5 males and 5 females, mean age 24.7 years, age range 21-36 years) participated in the experiment. All of them were native Italian speakers. Their educational level ranged from 13 to 19 years of schooling. No participant presented any neurological disease, major psychiatric disturbance or substance abuse, and none was being treated with psychoactive medication. All the subjects signed an informed consent form approved by the University of Modena Ethics Committee and were paid for their participation in the study. Handedness was assessed using the Edinburgh Handedness Inventory (17). We limited the study to right-handed subjects because language dominance is more consistently lateralised in this group of subjects. Indeed, in most right-handers (nearly 97%), the dominant hemisphere for language is the left one, while in left-handed subjects the language areas may be localised in the right (19%), the left (68%), or in both (13%) hemispheres (18).

Stimuli

Four types of stimuli were visually presented to the subjects during the experiment: Italian words, pronounceable pseudowords, strings of Italian consonants and strings of Japanese Hiragana letters. The Italian words were composed of 7 letters and 3 syllables. Half them had a low frequency of occurrence in the Italian language (frequency index between 0 and 2). The remaining were high frequency words (frequency values greater than 25) (19). The pseudowords were generated by substituting two letters in the normal words included in the experiment, and they all had three syllables but no meaning in the Italian language. Consonant strings consisted of 7 consonants. They were matched for visual length with five to six Hiragana fonts. In each experiment we used 60 stimuli for words and consonant strings and 30 stimuli for the other two categories (pseudowords and Hiragana strings).

Activation paradigm

Subjects received instructions and underwent brief practice sessions for each task before entering the scanner. During scanning, stimuli were back-projected onto the centre of an opaque screen located at the subject’s feet (viewing distance = 200 cm). They viewed the screen in a darkened room through a mirror placed over the birdcage radiofrequency coil of the scanner and responded using a custom-made response box with a two-position lever. The response box was connected, through a fibre optic system, to a Macintosh computer, running Superlab software (Cedrus Co, Silver Spring, MD, USA). Each stimulus was presented for 1700 ms and was followed by a 300 ms blank screen interval.

The activation paradigm (Fig. 1) included two conditions: lexical decision and graphemic decision. The lexical decision task required subjects to discriminate between words and pseudowords. Each lexical decision block included 10 words and 5 pseudowords. In the graphemic decision task, subjects had to distinguish Latin consonants from Japanese letters. Each block consisted of 10 strings of Latin consonants and 5 Hiragana strings. Lexical and graphemic decisions alternated three times in each run. Each subject was examined during 8 consecutive runs.

![Fig. 1 - Schematic representation of the activation paradigm that involved alternating graphemic and lexical decision tasks.]
fMRI and lexical decision

Image acquisition

Whole-brain fMRI was conducted on a commercial 1.5 Tesla scanner (Horizon Hispeed 77, Soft. rev. 5.5, Signa General Electric Medical Systems, Milwaukee). Echo-planar images were collected using a single shot, blipped, gradient echo-echo-planar pulse sequence developed by Peter Jezeard at the National Institutes of Health, Bethesda MD, USA (TR (repetition time) = 3300 ms; TE (echo time) = 42 ms, flip angle = 90°, FOV (field of view) = 240 x 240 mm, acquisition matrix = 64 x 64).

During each functional brain volume scanning, 16 contiguous 5-mm thick axial slices were selected to provide coverage of the entire brain (voxel size 3.75 x 3.75 x 5 mm). Before and after functional imaging, high resolution (0.94 x 0.94 mm in plane) 2D and 3D anatomical images were collected. Two-dimensional images were acquired with spoiled gradient-recalled at steady-state (GRASS) sequences, set as follows: TE = 9 ms, TR = 500 ms, flip angle = 90°, number of excitations (NEX) = 1, slice thickness = 5 mm, FOV = 240 x 240 mm, acquisition matrix = 256 x 256. For 3D acquisition, spoiled GRASS and inversion recovery sequences were used with the following parameters: TE = 24 ms; TR = 300 ms, flip angle = 20°; NEX = 1, slice thickness = 1.5 mm, FOV = 24 x 24, acquisition matrix = 256 x 192. Foam padding and an adjustable cotton strip were used to restrict head motion within the coil.

For each subject we collected 8 functional volume series. During each series, we acquired four dummy scans (to ensure steady magnetisation at the beginning of each series) and 60 sequential echo-planar images to be used in the subsequent analysis. Interscan interval (TR) was 3.3 s. A series consisted of 3 cycles during which two tasks alternated in a fixed order. Each cycle consisted of two 33-s epochs during which subjects performed either the lexical decision or the graphemic decision task. Ten functional images were collected for each epoch. Consequently, total scanning duration for each series was 3 min and 30 s.

Data analysis

Image reconstruction and analysis were performed on a Sun Sparc5 workstation. The data were analysed with SPM96 and SPM97 developed at the Wellcome Department of Cognitive Neurology in London (20).

The analysis included three steps. First of all, the images of each subject were realigned to the thirtieth volume of the fourth run in order to minimise artefacts produced by subjects’ movements. Then images were transformed in the standard anatomical space of Talairach and Tournoux (21). This reduced inter-subject variability and allowed us to perform group analysis. Normalised images were smoothed using a Gaussian filter with 8-mm kernel in order to improve signal to noise ratio and to obtain a data distribution that was closer to a Gaussian field model. This allowed us to carry out a covariance analysis on a voxel by voxel basis.

Task-specific brain activation was assessed by using the t statistic, thus generating statistical parametric maps of t-values (SPM(t) maps), which were transformed to Z distribution (SPM(Z) maps) reflecting differences between two conditions at each voxel location. Statistical significance was thresholded at p=0.001, which corresponds to a Z value of 4.15. The statistical map obtained was corrected for multiple non-independent comparison (p=0.05).

To detect areas of significant activation in each single subject we chose a p value of 0.01 with a spatial extent of at least 8 voxels. This approach minimised the type I error (i.e., the risk of false positive activation). However in a clinical setting it might be wiser to adopt the opposite approach, i.e., to minimise the risk of missing areas that might be important for language processing. For this reason we also performed three further analyses: one in which we varied the spatial extent (4 voxels) but left the same p value and another two in which we set p value at 0.05 and chose a spatial extent of 4 and 8 voxels respectively. Furthermore, we performed a conjunctural analysis to identify areas commonly activated in all subjects using a p value of 0.1.

Results

Behavioural data

All the subjects performed the two tasks without difficulty, giving 99% correct answers during the lexical decision task and 99.3% during the graphemic decision task. Figure 2 (see over) shows the mean response times on the two tasks and with the different kinds of stimuli. Response times were compared with a repeated measure ANOVA after eliminating values exceeding ± 2 SD each individual subject’s average. The results demonstrated that lexical decision-making was significantly slower than graphemic decision-making (F = 88.8, d.f. = 9, p < 0.0001). Decisions relating to words were made more quickly than decisions relating to pseudowords (F = 43.3, d.f. = 9, p = 0.0001) and there was also significant difference between Hiragana and consonant strings (F = 13.3, d.f. = 9, p = 0.005)

Neuroimaging data

The experimental paradigm that we devised was based on cognitive subtraction. We hypothesised that, after subtracting graphemic decision-related activation from that related to the lexical decision we would eliminate visual and motor components not related to the linguistic function.

The group analysis (Table 1, see over, Fig. 3, see p. 188) showed 8 cerebral regions that were activated during the lexical decision task relative to the graphemic decision task. The largest of these was located in the occipital cortex. This region included the lingual gyrus bilaterally (BA 18), the left fusiform gyrus (BA 18/19) and the left inferior occipital gyrus (BA 18). Moreover, in the left hemisphere, this region extended to the temporal cortex, where three activated areas were identified in the superior (BA 22), in the middle (BA 21) and in the inferior (BA 37) temporal gyrus. An area in the right cerebellum was also activated. Significant activation was also demonstrated in the left superior occipital gyrus and in the angular gyrus (BA 19/39), in the left inferior parietal lobule (BA 40), and in the superior temporal gyrus (BA 38) on both sides. The inferior frontal gyrus (BA 44) was also activated bilaterally, but the region in the left hemisphere was wider and...
gave a higher Z score. This region also included the a-
terior part of the left inferior frontal gyrus (BA 45) and
an area in the left precentral gyrus (BA 6). The last re-
gion included part of the left superior frontal (BA 8) and
the left dorsolateral prefrontal cortex (BA 6).
Single subject analysis (Table 2, see over) showed
highly significant activity in nine subjects in the left tem-
poral lobe including the superior (BA 38/22) and the
middle (BA 21) temporal gyrus.
In two subjects an area in the right superior temporal
 gyrus (BA 38) was also identified.
Peaks of activation in the left frontal gyrus were ob-
served in 7 subjects. In two of them peaks were situat-
ed in the posterior part (BA 44) of the inferior frontal re-
gion, in three the anterior part of the same region was
activated (BA 45). The last two subjects presented sig-
nificant cerebral activity in both these areas (BA 44-45).
Two subjects showed significant activation in the right
inferior frontal gyrus.
The left parietal lobule (BA 40) was activated in 4 sub-
jects, the superior occipital gyrus in 1 subject, while
peaks of activation were situated in different parts of
the largest region identified by the group analysis in
eight subjects. Activity was localised in the right lingual
gyrus in two of them, in the lingual gyrus of both the
hemispheres in another four and in the fusiform gyrus
in only one subject. The last subject presented a peak
of activation only in the right cerebellum.
When we performed a single subject analysis using a
spatial extent of 4 voxels with a p value of 0.01, one
more subject presented an area of activation in the su-
perior temporal gyrus, so that in all ten subjects activity
was revealed in the temporal region.
When applying a p value of 0.05 and a spatial extent of
4 voxels, the left inferior frontal gyrus was found to be
activated in 8 subjects.
In the single subject analysis we found differences in
the activation patterns among subjects, as we had sub-
jects who presented activation in all the areas shown in
the group analysis, and others with only a few regions
activated.
To identify areas similarly activated in all the subjects, we
performed a conjunction analysis. This analysis identified
two cerebral regions: the left inferior frontal gyrus and the
left middle temporal gyrus (Table 3, see over).
Discussion
Successful and reliable fMRI in a clinical population re-
quires a careful analysis of a task’s characteristics in nor-
mal subjects. First of all, the activation task has to be
simple enough even for brain-damaged subjects to per-
form with a minimal number of errors. Also, the task
should be sensitive enough to activate areas that are in-
volved in the targeted process but it should not engage
areas unrelated to the cognitive component to be studied
(e.g., attentional networks, primary sensory, and motor
areas). Finally, the experimental setting should allow the
monitoring of subjects’ performance during scanning.
Group analysis demonstrated that the experimental
paradigm we propose is sensitive enough to localise
the cerebral regions involved in the making of lexical
decisions relating to visually presented words. The al-
ternation of lexical and graphemic decisions is a simple
procedure that can be easily administered to a wide
range of brain-damaged patients while also allowing close monitoring of their performance. With this method we identified several areas likely to be related to different aspects of language processing, such as recognition of written word form (orthographic component), speech sound processing (phonological component), and word meaning processing (semantic component).

Insights into the role of specific regions may be obtained from previous neuroimaging studies. In the following discussion we will compare our findings with those obtained by previous neuroimaging studies of language processing.

Several groups (14,22,23) found that the extrastriate cortex is involved in the perception of the visual word form. On the contrary other studies localised the same function in the left middle and inferior temporal gyrus (15,24,25). Indeed, it has been observed that the extrastriate cortex is also activated in object perception (26-28). In our study, the activation encompassed a wide region including the temporal cortex, the fusiform, and the lingual gyrus. As the control task also required visual recognition (of letters), we would argue that all these areas are specifically involved in visual word form recognition and not only in visual recognition per se.

As noted by Price (29), the posterior basal part of the temporal lobe (BA 37) is activated by the phonological processing required in different tasks, such as reading words, and naming objects, colours, and letters. The left inferior parietal lobule (BA 40) is also commonly related to phonological processing. Price (29) noted that this area is activated more during the reading of pseudowords than when reading words. Moreover, both studies on brain-damaged patients (30) and neuroimaging data (11) provide converging evidence that assigns a pivotal role to this region in subserving the “phonological store” component of the working memory.

We also found activation of the right cerebellar hemisphere and of the left inferior frontal gyrus (BA 44 and 45). Neuroimaging studies (12,28,31) suggest that these two regions can be involved together in the semantic components of language processing. It has

Table I - Stereotactic locations of cluster maxima of the group analysis.

<table>
<thead>
<tr>
<th>Region of activity</th>
<th>Anatomical Region</th>
<th>Side</th>
<th>BA</th>
<th>Coordinates x y z</th>
<th>Maximum Z score</th>
<th>No. of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lingual gyrus</td>
<td>Right</td>
<td>18</td>
<td>-76</td>
<td>8</td>
<td>8.01</td>
<td>722</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>Left</td>
<td>22</td>
<td>-44</td>
<td>-60</td>
<td>7.94</td>
<td></td>
</tr>
<tr>
<td>Lingual gyrus</td>
<td>Left</td>
<td>18</td>
<td>-80</td>
<td>-12</td>
<td>7.89</td>
<td></td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>Left</td>
<td>19</td>
<td>-44</td>
<td>-24</td>
<td>7.75</td>
<td></td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>Left</td>
<td>21</td>
<td>-44</td>
<td>-60</td>
<td>7.70</td>
<td></td>
</tr>
<tr>
<td>Inferior temporal gyrus</td>
<td>Left</td>
<td>37</td>
<td>-52</td>
<td>-52</td>
<td>7.46</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Right</td>
<td>8</td>
<td>-76</td>
<td>-16</td>
<td>7.37</td>
<td></td>
</tr>
<tr>
<td>Inferior occipital gyrus</td>
<td>Left</td>
<td>18</td>
<td>-88</td>
<td>-32</td>
<td>7.14</td>
<td></td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>Left</td>
<td>18</td>
<td>-72</td>
<td>-8</td>
<td>6.96</td>
<td></td>
</tr>
<tr>
<td>2 Inferior frontal gyrus</td>
<td>Left</td>
<td>44</td>
<td>-24</td>
<td>-52</td>
<td>7.69</td>
<td>256</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>Left</td>
<td>45</td>
<td>-28</td>
<td>-52</td>
<td>7.45</td>
<td></td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>Left</td>
<td>6</td>
<td>28</td>
<td>-44</td>
<td>7.36</td>
<td></td>
</tr>
<tr>
<td>3 Superior temporal gyrus</td>
<td>Left</td>
<td>38</td>
<td>-8</td>
<td>-56</td>
<td>7.00</td>
<td>26</td>
</tr>
<tr>
<td>4 Superior frontal gyrus</td>
<td>Left</td>
<td>8</td>
<td>48</td>
<td>-4</td>
<td>6.96</td>
<td>40</td>
</tr>
<tr>
<td>Dorsal frontal gyrus</td>
<td>Left</td>
<td>6</td>
<td>52</td>
<td>-4</td>
<td>5.88</td>
<td></td>
</tr>
<tr>
<td>5 Inferior parietal lobule</td>
<td>Left</td>
<td>40</td>
<td>44</td>
<td>-44</td>
<td>6.39</td>
<td>19</td>
</tr>
<tr>
<td>6 Superior occipital gyrus/ angular gyrus</td>
<td>Left</td>
<td>19/39</td>
<td>-76</td>
<td>24</td>
<td>6.27</td>
<td>27</td>
</tr>
<tr>
<td>7 Superior temporal gyrus</td>
<td>Right</td>
<td>38</td>
<td>12</td>
<td>52</td>
<td>5.89</td>
<td>13</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>Right</td>
<td>47</td>
<td>16</td>
<td>-4</td>
<td>5.37</td>
<td></td>
</tr>
<tr>
<td>8 Inferior frontal gyrus</td>
<td>Right</td>
<td>44</td>
<td>28</td>
<td>44</td>
<td>5.25</td>
<td>10</td>
</tr>
</tbody>
</table>

Location coordinates are reported in mm according to the stereotactic atlas of Talairach and Tournoux (1988): x (- is left, + is right), y (- is posterior to the anterior commissure line, + is anterior to the anterior commissure line), and z (- is inferior to the intercommissural line, + is superior to the intercommissural line). p = 0.05, corrected. BA = Brodmann area.
been reported that patients with lesions in the right cerebellum can display linguistic disturbances typical of left frontal region damage (12). Yet, the reason why this does not happen more often in patients with right cerebellar damage is far from clear.

There is considerable debate about the role of the left inferior frontal cortex in written language processing. In our study we found activation including both the anterior triangular part (BA 45) and the posterior opercular portion (BA 44) of this region. The prevailing view is that the anterior/ventral part of the inferior frontal gyrus (corresponding to BA 45) is more active during tasks involving semantic classifications or generalisation of semantic association. On the other hand, the posterior part of this region (BA 44) is engaged by phonological processes occurring during both semantic and phonological tasks or by tasks that involve the verbal working memory (11,12).

In our sample of right-handed subjects, the inferior frontal cortex was activated not only on the left but also, although to a lesser extent, on the right side. It has been argued (32) that the two hemispheres may process written information in different ways, the right hemisphere processing small units (phonemes) and the left hemisphere being involved in processing larger units (syllables and rhymes). However, previous studies found frontal bilateral activation in both semantic and phonological processes (13,22). Our study cannot tell us whether the activation we found is due to different hemispheric processing styles or to a co-operation of homologous areas of both hemispheres in some aspects of language processing.

Semantic processing required by the lexical decision task probably also activated the region including the left angular gyrus (BA 39) and left superior occipital gyrus (BA 19). In agreement with this interpretation, the same areas were activated in a couple of previous studies that compared a semantic decision task and a phonological discrimination task (29,33). A similar function has been assigned (29) to the anterior part of the superior temporal gyrus (BA 38).

In conclusion, our results are in agreement with other neuroimaging studies. Any discrepancy in the number, in the precise localisation, and in the attribution of a specific role to the areas identified by different studies,
### Table II - Single subject analysis. The table indicates the number of subjects showing regions of activity, identified with the group analysis, at different p values and spatial extents

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>BA</th>
<th>p=0.01 8 voxels</th>
<th>p=0.01 4 voxels</th>
<th>p=0.05 8 voxels</th>
<th>p=0.05 4 voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Occipital cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lingual gyrus</td>
<td>18</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Right lingual gyrus</td>
<td>18</td>
<td>6</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Left fusiform gyrus</td>
<td>19</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Left middle occipital gyrus</td>
<td>19</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Temporal cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left sup. temporal gyrus</td>
<td>38/22</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Left middle temporal gyrus</td>
<td>21</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Left middle and superior temporal gyrus</td>
<td>21-38</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Right sup. temporal gyrus</td>
<td>38</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Parietal cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left parietal lobule</td>
<td>40</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Frontal cortex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>44</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>45</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>44-45</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Right inferior frontal gyrus</td>
<td>44</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Left superior frontal gyrus</td>
<td>8</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Left frontal dorsal gyrus</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: BA = Brodmann area

### Table III - Conjunction analysis. Cerebral areas commonly activated in all the subjects (p=0.1)

<table>
<thead>
<tr>
<th>Region of activity</th>
<th>Anatomical Region</th>
<th>Side</th>
<th>BA</th>
<th>Talairach Coordinates</th>
<th>Maximum Z score</th>
<th>No. of voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x  y  z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Inferior frontal gyrus</td>
<td>Left</td>
<td>44</td>
<td>-48 8 20</td>
<td>8.10</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Middle temporal gyrus</td>
<td>Left</td>
<td>21</td>
<td>-56 8 -8</td>
<td>7.27</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>Gyrus cinguli</td>
<td>Right</td>
<td>32</td>
<td>8 16 40</td>
<td>4.81</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Inferior frontal gyrus</td>
<td>Right</td>
<td>44/45</td>
<td>52 24 16</td>
<td>3.70</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>Middle temporal gyrus</td>
<td>Right</td>
<td>21</td>
<td>56 12 -8</td>
<td>3.57</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Inferior temporal gyrus</td>
<td>Left</td>
<td>45/47</td>
<td>-36 16 4</td>
<td>3.43</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Cuneus</td>
<td>Left</td>
<td>19</td>
<td>-16 -88 32</td>
<td>3.33</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>Thalamus</td>
<td>Left</td>
<td>-24</td>
<td>-12 4</td>
<td>2.97</td>
<td>25</td>
</tr>
</tbody>
</table>

Abbreviation: BA = Brodmann area
can be explained by differences in the statistical treatment of the data, in the anatomical structure of the subjects and in the tasks adopted. Conjunction analysis showed two areas similarly activated in all the subjects: the left inferior frontal gyrus and the left middle temporal gyrus. We would argue that these two areas are the ones most necessary to perform the task, while the remaining areas are variably activated in each subject according to the strategy adopted, which may engage different cerebral networks.

Results of the single subject analysis proved that our paradigm can reveal areas involved in language processing even in single individuals. This is one of the most crucial aspects as regards the possible application of the paradigm in a clinical setting. Since there is no standard for the statistical treatment of data in clinical settings, we performed two single subject analyses, applying different significance thresholds. With a p value of 0.01, significant variation of the magnetic signal was demonstrated in the left temporal region in 9/10 subjects, and in the left inferior frontal gyrus and in the occipital areas in 7/10 subjects. With a p value of 0.05 activation in the language-related areas was demonstrated in a larger number of subjects, and a few areas of activation not identified in the group analysis were also found. Basically the two thresholds differ in their relative weight on Type I and on Type II error. With p=0.01, false positive localisation is most unlikely, but there is a greater risk of missing areas that are involved in the targeted processes. With p=0.05, the opposite risk (i.e., of including unrelated areas) increases, while it becomes unlikely that relevant activation will be missed. This latter approach is preferable in situations when presurgical localisation of the linguistic areas is needed. On the contrary, when it is a case of studying areas that are involved in recovery after brain damage, a stricter criterion might be needed.

The results of single subject analysis were variable. A number of subjects showed patterns of activation including the same anterior and posterior cerebral regions that were activated in the group analysis, while other subjects apparently only needed a few areas to perform the task. In performing a cognitive task it is always possible that areas are activated that are not specifically involved in the targeted functions (e.g., those involved in attentional processes).

Behavioural data analysis demonstrated that reaction times were slower for lexical than for graphemic decisions. However, subjects performed both tasks correctly and there were no differences in the number of errors in the two tasks. Also, neither group nor single subject analysis demonstrated activation in those areas (e.g., the anterior cingulate gyrus) that are commonly related to attentional effort. As a consequence we would argue that differences found in the activation maps of different subjects could be better explained by differences in the task execution strategy.

The purpose of this study was to validate a paradigm to be used in clinical settings that could activate a large number of areas involved in language function without activating regions unrelated to language processing. Indeed, we found that, even in single subjects, our paradigm is both sensitive and specific enough to localise several language-related areas. Further, it allows the monitoring of subjects’ performance, which is a fundamental requirement for any clinical application. However, the present study is limited by the relatively small size of the sample we tested and also by the fact that we still have to extend the study to a clinical population. On a more theoretical level it is also limited by the fact that brain regions mapped by PET and fMRI may not coincide with those that are necessary to perform the task that is targeted by the activation paradigm. Indeed, a number of non-specific areas (e.g., those involved in attention) might be activated as well.

To promote a more widespread clinical application of this paradigm, and of fMRI techniques generally, the next step is to test it on patients and to compare it with other techniques used for localising cognitive functions. Previous studies have demonstrated a substantial agreement between fMRI, PET and the Wada test in localising the dominant cerebral hemisphere for language. However, further investigations are needed in order to compare activation maps in each hemisphere. Also, the use of multiple language tasks should help to improve assessment of areas involved in language processing.

References

4. Brockway JP. Two functional magnetic resonance imaging fMRI tasks that may replace the gold standard, Wada testing, for language lateralization while giving additional localization information. Brain Cogn 2000;43:57-59


14. Petersen SE, Fox PT, Snyder AZ, Raichle ME. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. Science 1990;249:1041-1044


