Variability of fMRI Activation During a Phonological and Semantic Language Task in Healthy Subjects

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Abstract: Assessing inter-individual variability of functional activations is of practical importance in the use of functional magnetic resonance imaging (fMRI) in a clinical context. In this fMRI study we addressed this issue in 30 right-handed, healthy subjects using rhyme detection (phonologic) and semantic categorization tasks. Significant activations, found mainly in the left hemisphere, concerned the inferior frontal gyrus, the superior/middle temporal gyri, the prefrontal cortex, the inferior parietal lobe, the superior parietal lobule/superior occipital gyrus, the pre-central gyrus, and the supplementary motor area. Intensity/spatial analysis comparing activations in both tasks revealed an increased involvement of frontal regions in the semantic task and of temporo-parietal regions in the phonologic task. The frequency of activation analyzed in nine regional subdivisions revealed a high inter-subject variability but showed that the most frequently activated regions were the inferior frontal gyrus and the prefrontal cortex. Laterality indices, strongly lateralizing in both tasks, were slightly higher in the semantic (0.76 ± 0.19) than the phonologic task (0.66 ± 0.27). Frontal dominance indices (a measure of frontal vs. posterior left hemisphere dominance) indicated more robust frontal activations in the semantic than the phonologic task. Our study allowed the characterization of the most frequently involved foci in two language tasks and showed that the combination of these tasks constitutes a suitable tool for determining language lateralization and for mapping major language areas. *Hum Brain Mapp* 23:140–155, 2004.

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INTRODUCTION

Neuroimaging studies have proved successful in mapping different fields of human cognition using different processing tasks in healthy and brain-damaged subjects. However, with the increasing number of functional studies, one may observe that with similar or even identical experimental paradigms, the results may be quite different from one study to another [Cabeza and Nyberg, 2000], suggesting that different sources of variability exist in neuroimaging investigations. One of the major problems raised by the variability of activated regions is the extreme difficulty to extract the areas that are truly relevant for the considered function [Bub, 2000; Humphreys and Price, 2001]. For this purpose, some authors have conducted meta-analysis on the results reported by different groups in order to determine the most frequently activated regions for a given cognitive process [Cabeza and Nyberg, 2000; Poline et al., 1996; Turkeltaub et al., 2002].

Among the different factors that may account for the variability of activation in functional studies, inter-individual anatomo-functional differences [Ojemann et al., 1989; Rademacher et al., 1993; Steinmetz and Seitz, 1991] and individual cognitive strategies [Nadeau et al., 1998] are considered as primordial. Concerning language studies in particular, the “subject factor” has direct consequences on language representation in the brain. In fact, subjects with the same handedness may show a left hemisphere (LH) dominance, a right hemisphere (RH) dominance, or even bilateral language representation [Binder et al., 1996; Knecht et al., 2000b]. In addition, one may also include gender differences [Phillips et al., 2001; Pugh et al., 1996; Shaywitz et al., 1995b], subject’s age [Vandenbroucke et al., 2004], native language differences [Chee et al., 2001] and structural differences in the language regions [Amunts et al., 1999; Steinmetz and Seitz, 1991]. In this respect, group analyses, which neglect the subject factor and extract only the collective effects of neural activations that are spatially coincident across subjects, provide little detail about individual variability in the functional organization of the human brain.

In order to limit the influence of these factors, different analysis approaches have been proposed, the aim being to precisely define the location of critical language areas in the normal brain. Critical language areas, also termed by some authors as essential, relevant or epicenters, refer to brain regions implicated in both language production and comprehension processes [Papathanassiou et al., 2000], and whose damage would lead to language impairment [Ojemann et al., 1989]. Conjunction analysis was thus used to provide the anatomo-functional definition of language epicenters [Papathanassiou et al., 2000]. The combined task analysis, based on the definition of activations revealed by more than one single task [Ramsey et al., 2001], aimed to minimize variance across subjects. Finally, reproducibility analysis has also recently been proposed to assess the reliability of individual activations [Maldjian et al., 2002; Rutten et al., 2002a].

Assessing the inter-individual variability of activation is a critical issue when addressing the question of brain organization in patients following brain damage. Prior to neurosurgery, it is thus crucial to determine those activations that fit with “normal” patterns and those due to neural networks reorganization in patients with long-lasting epilepsy or with other developing diseases (e.g., tumors). However, despite its clinical importance, the question of variability of activation in healthy subjects has been addressed in a few studies that used either one [Burton et al., 2001; Herholz et al., 1996; Xiong et al., 2000] or two language tasks [Maldjian et al., 2002; Nadeau et al., 1998; Tzourio-Mazoyer et al., 2004]. In this study, we used two language tasks, addressing two different aspects of language processing in order to determine language areas in the group brain and to assess inter-individual variability across the two tasks. The use of two tasks allows for particularly reducing any potential intersession variability [McGonigle et al., 2000], especially with regard to the temporo-parietal regions [Fernandez et al., 2003]. The rhyme detection task (referred to as the “phonological task”) used here, presupposes a grapho-phonemic conversion of the written words in order to detect rhyming. The second, the semantic judgment task, requires not only transcoding from print to phonology but additionally the activation of word representations in order to decide if the two words belong to the same semantic category or not. In previous studies, both tasks have been shown to provide robust LH activation [Baciu et al., 2001; Billingsley et al., 2001; Kareken et al., 2000; Khateb et al., 1999; Lurito et al., 2000; McDermott et al., 2003; Pugh et al., 1996; Seghier et al., 2001; Shaywitz et al., 1995a,b]. In addition, some studies have also suggested that these two tasks can induce different activation patterns, especially with respect to frontal and temporal regions [Billingsley et al., 2001; Pugh et al., 1996]. As a baseline, both tasks used a perceptual comparison condition, similar to other control conditions used in previous reports (such as line orientation, letters matching, false fonts matching or symbol sequence judgment tasks) [Baciu et al., 2001; Billingsley et al., 2001; Lurito et al., 2000; Pugh et al., 1996]. Our results are discussed in the light of previous functional language studies.

SUBJECTS AND METHODS

Subjects

Thirty healthy, right-handed subjects (20 men, 10 women; mean age 29 ± 11 years) from the hospital and medical school participated in this study after having provided their informed consent as recommended by the ethical committee of the Geneva University Hospitals. Subjects were native French speakers and had no history of neurological or psychiatric diseases. All had normal or corrected-to-normal vision.

Paradigm and Stimuli

For the two experiments, a block paradigm that alternated between “control” and “activation” sequences was applied.

The stimuli, concrete imaginable nouns of high-frequency French word pairs, were selected from a French table for word frequency [Content et al., 1990] and were simultaneously presented to the subjects via a video projector, a front-projection screen and a system of mirrors fastened to the head coil. The visual field spanned by this setup was approximately 15×11 degrees. In the phonologic task (rhyme detection), the activation condition was constituted of 60 word pairs (40 rhyming pairs and 20 non-rhyming pairs) and the subjects had to give a response (with the right hand) only if the two words in each pair rhymed (go/no-go task). In the semantic task (semantic categorization), the activation condition was comprised of another set of 60 word pairs that were either categorically related (i.e., two words were exemplars of the same semantic category, 40 pairs) or unrelated (the two words belonged to two different semantic categories, 20 pairs). The subjects again performed a go/no-go task and responded whenever words were exemplars of the same semantic category [Seghier et al., 2001]. In both tasks, the control condition that alternated with the activation condition consisted of a perceptual categorization task in which pairs of either visually similar meaningless Greek letter-strings (40 pairs) or visually different strings (20 pairs) were presented to the subjects. In order to maintain the rate of motor responses constant as in activation conditions, the subjects had to respond only if the two strings in each pair were visually identical. In all conditions (both activation and control conditions in both tasks), stimulus pairs were presented every 2 s on the screen for 600 ms and in blocs of 24 s, repeated 5 times per condition. Accordingly, alternating blocs of activation-control conditions yielded a total duration of 4 min per task. Responses were given by pushing an air-mediated button and the experimenter recorded the performance of the subject. In order to ensure that the task was correctly understood, all subjects were provided with detailed instructions before entering the scanner and underwent a short training session.

MRI Acquisition

Experiments were performed on a 1.5T ECLIPSE system (Marconi/Philips, Cleveland, OH) using the standard head coil configuration. Acquired multi-slice volume was positioned on sagittal scout images. Before the functional MR scans, an anatomical scan (a GRE T1-weighted sequence, TR/TE/Flip = 162 ms/4.47 ms/80°, FOV = 250 mm, matrix = 256×256 , slice-thickness = 5 mm) was performed to acquire the same volume as in the functional session. Anatomical reference images, acquired after the functional scans, consisted of a 3-D GRE T1-weighted sequence (TR/TE = 15 ms/5 ms, FOV = 250 mm, matrix = 256×256 , slice-thickness = 1.25 mm). Functional imaging consisted of an EPI GRE sequence (TR/TE/Flip = 2 s/40 ms/80°, FOV = 250 mm, matrix = 128×128 , 17 contiguous 5-mm axial slices). The explored volume was measured twelve times during each condition of the paradigm. Functional scanning was always preceded by 10 s of dummy scans to insure tissue steady-state magnetization.

Data Analysis

Data processing relied upon cross-correlation analysis [Bandettini et al., 1993] after motion correction [Woods et al., 1992] using MEDx software (version 3.40; Sensor Systems, Sterling, VA). Data were smoothed spatially by convolution with a Gaussian kernel ($6 \times 6 \times 6$ mm³). The cross-correlation, as a Z-value, was calculated pixel-wise between a delayed box-car function and the set of measurements, after auto-correlation correction (4 s) [Friston et al., 1995]. Afterwards, the statistical distribution of the Z-values was calculated and a probability value for each Z-value was attributed. This approach allows the use of the same probability level for each experiment and thus provides a higher accuracy when addressing the question of reproducibility [Moser et al., 1996]. Only clusters of more than four statistically significant ($P < 0.005$) pixels were considered [Forman et al., 1995]. Individual Z-score maps were normalized to the Talairach and Tournoux's [1988] space and averaged [Bosch, 2000] in order to show major activated foci in each task. The normalization procedure used in MEDx consisted of the application of an affine transformation following identification of eight anatomical landmarks (including the anterior and posterior commissures points).

In order to assess possible spatial differences between the two tasks, the individual x , y , and z Talairach coordinates were first reported for each activated region. Activated regions, defined as separate activated clusters on the functional map of each subject, were identified according to their relative Talairach coordinates and their corresponding anatomical landmarks. Mean (and standard deviations) of x , y , z Talairach coordinates were then computed and compared between the tasks. In addition, an Euclidean distance was computed between the mean locations in the rhyme and the semantic task.

For statistically assessing possible intensity and/or spatial differences between the two tasks, we computed a voxel-by-voxel paired t -test analysis on individual Z-score maps [Bosch, 2000] (i.e., for each voxel, we computed a paired t -test between individual Z-scores obtained in the phonologic task and Z-scores obtained in the semantic task).

For assessing inter-individual variability, we relied on previous studies using the frequency of occurrence for each observed region [Vandenbroucke et al., 2004; Xiong et al., 2000; Zahn et al., 2004]. This frequency, which refers to how often a given region was activated within the group in each task, was compared between the two tasks. Afterwards, two activation indices were calculated for each subject in each task. The laterality index (LI), which varies from +1 (for LH lateralization) to -1 (for RH lateralization), was computed using the total number of significantly activated pixels in each hemisphere ($LI = (\text{left pixels} - \text{right pixels}) / (\text{left pixels} + \text{right pixels})$) [Binder et al., 1996; Hinke et al., 1993]. A mean LI (and standard deviation) was then computed for each task by averaging individual LIs in order to determine a threshold for left and atypical language lateralization. For this study, we used all subjects' normative values to determine a short-cut at the mean minus 2 standard deviations

(instead of any other arbitrary value such as 0.2 used in some previous studies, see Springer et al. [1999]).

In addition to the LI, a second index, referred to as a “frontal dominance index” (FDI), was calculated so as to determine the extent of left frontal lobe (anterior) as compared to left temporo-occipito-parietal (posterior) activations. The computation of this index was first motivated by the fact that some previous studies have claimed that strong left lateralization indexes were obtained in tasks implicating preferentially frontal regions [e.g., Lehericy et al., 2000; Spreer et al., 2002]. This analysis thus sought to verify whether a high LI in one task can be explained by a high FDI on the same task. Practically, for voxel counting, both the frontal (or anterior) and the posterior volumes were delimited by cubic boxes in the left hemisphere (Talairach dimensions for the anterior box: $x = -70$ to 0 mm, $y = -10$ to 76 mm, $z = -30$ to 68 mm and Talairach dimensions for the posterior box: $x = -72$ to -2 mm, $y = -106$ to -12 mm, $z = -30$ to 68 mm). The FDI ($\text{FDI} = (\text{left frontal pixels} - \text{left posterior pixels}) / (\text{left frontal pixels} + \text{left posterior pixels})$), calculated in the same manner as the LI, thus yields positive values for left frontal dominance and negative values for left temporo-posterior dominance.

RESULTS

Due to acquisition problems in three subjects (one subject in the rhyme task and two subjects in the semantic task) and the fact that one other subject decoded Greek letter strings in the control condition, 26 of 30 subjects were included in the following analysis.

Subject Performance

Accuracy (correct go and no-go responses) in each task and in each condition (i.e., activation vs. control conditions) was analyzed in all subjects in order to ensure the feasibility of the tasks in the scanner and to assess the tasks’ difficulty. In the phonologic task, this analysis revealed a mean accuracy ($\pm$ SD) of $82 \pm 12\%$ in the rhyme detection condition (activation) and of $92 \pm 5\%$ in the visual perceptual categorization (control) condition. In the semantic task, mean accuracy ($\pm$ SD) was $83 \pm 13\%$ in the semantic categorization condition and $93 \pm 6\%$ in the control condition. A 2×2 repeated measures analysis of variance using task (2 tasks) and condition (2 conditions) as within-subjects factors only showed a highly significant main effect for condition ($F(1, 25) = 40.2$, $P < 0.00001$), without an interaction between the two analysis factors. This analysis confirmed the absence of difference in terms of task difficulty and indicated that the control condition (categorization of meaningless visual stimuli) was easier to perform in both tasks than the activation conditions.

fMRI Average Activation

As depicted in Figure 1, statistically significant activations for the two tasks were found mainly in the LH. Some subjects showed additional significant activations in the RH,

however these were not very frequent and were thus not evident in the averaged map. The activation in the rhyme (Fig. 1A) and the semantic task (Fig. 1B) globally displayed involvement of the inferior and middle frontal regions, the temporal and the occipito-parietal areas. The detailed analysis of individual maps in both tasks allowed for the identification of nine regional subdivisions distributed in five different brain areas. These included: (1) the inferior frontal gyrus (IFG, Broca’s area); (2) the mid-dorsolateral prefrontal cortex (MDPFC) and (3) the posterior prefrontal cortex (PPFC) in the prefrontal cortex; (4) the superior (STG) and (5) the medial temporal gyrus (MTG) in the temporal cortex; (6) the inferior parietal lobule (IPL) and (7) the superior parietal lobule/superior occipital gyrus (SPL) in the occipito-parietal cortex; (8) the pre-central gyrus (PCG) and (9) the medial frontal cortex (or supplementary motor area, SMA) in the motor cortex.

Differences Between Tasks

Table I reports the mean ($\pm$ SD) x , y , and z coordinates computed on the basis of individual responses for each one of the 9 subdivisions in each task. These coordinates suggest that, despite a considerable overlapping between the activations in the rhyme and the semantic tasks, some regions displayed slight spatial differences. These differences are illustrated in Figure 2A, which plots the mean location for each activated regional subdivision in each task in terms of the y and z axis. Figure 2B, which displays the Euclidean distance computed between the mean locations in the rhyme and the semantic task, indicates that the highest spatial overlapping concerned the activations found in the STG and that the largest spatial differences concerned the activation found in the inferior parietal lobule (IPL).

Given the fact that the averaged maps did not show significant activations in the RH, the voxel-by-voxel analysis performed to assess intensity/and or spatial (location) differences was applied only on LH voxels. This analysis showed significant differences (region size = > 10 pixels at $P < 0.01$) mainly in the areas observed on the averaged maps in both tasks. The phonologic task preferentially involved voxels in: the superior temporal gyrus (x, y, z coordinates = $-38, -54, 16$; $P < 0.0001$); the superior frontal gyrus ($x, y, z = -26, 44, 32$, $P < 0.0001$), the inferior parietal lobule ($x, y, z = -52, -38, 36$; $P < 0.0005$), the superior parietal/occipital cortex ($x, y, z = -22, -78, 46$; $P < 0.0001$), and the SMA ($x, y, z = -8, -2, 56$, $P < 0.0005$). The semantic task on the other hand preferentially involved voxels in: the inferior frontal gyrus ($x, y, z = -48, 28, 2$; $P < 0.0001$) and in the dorsolateral prefrontal cortex ($x, y, z = -52, 20, 20$; $P < 0.005$).

Frequency of Activation

The variability of activation between subjects in each task was first assessed by determining the frequency of activation in each region and regional subdivision. Given the fact that the same regional subdivisions were activated in both tasks at the group level, the comparison of the frequency of activation for the same region between the two tasks al-

A***Rhyme Detection*** **B*****Semantic Categorization*** **Figure 1.**

Average activation during the rhyme detection (**A**) and the semantic categorisation task (**B**). These group-averaged maps indicate the predominant activation of frontal areas in both tasks but also of temporal, occipito-parietal, and motor regions. Slices were

taken from the position -8 to $+48$ in the z dimension of the Talairach space. Yellow colour indicates high statistical significance.

TABLE I. The five major cortical regions, their subdivisions, and the corresponding Brodmann areas with their mean ($\pm$ SD) x, y and z coordinates in the rhyme and the semantic task

Regions/subdivisions	Brodmann Area	Coord. rhyme (x; y; z)	Coord. semantic (x; y; z)
Inferior frontal gyrus			
Broca area	44/45/47	-47 ± 8 ; 15 ± 9 ; 16 ± 10	-46 ± 6 ; 19 ± 7 ; 12 ± 11
Prefrontal cortex			
Mid-dorsolateral prefrontal cortex	46/9	-44 ± 6 ; 31 ± 5 ; 27 ± 7	-45 ± 5 ; 29 ± 4 ; 22 ± 5
Post. prefrontal cortex	9/44	-45 ± 5 ; 12 ± 3 ; 33 ± 4	-44 ± 6 ; 14 ± 5 ; 32 ± 4
Temporal gyrus			
Sup. temporal gyrus	22/42	-54 ± 8 ; -35 ± 8 ; 11 ± 6	-53 ± 8 ; -35 ± 12 ; 10 ± 6
Med. temporal gyrus	21/22	-55 ± 2 ; -35 ± 10 ; 3 ± 5	-55 ± 3 ; -41 ± 14 ; 3 ± 6
Occipito-parietal regions			
Inf. parietal lob.	39/40	-38 ± 13 ; -49 ± 11 ; 37 ± 6	-34 ± 4 ; -56 ± 9 ; 42 ± 5
Sup. parietal lob./Sup. occip. gyrus	7/19	-22 ± 7 ; -72 ± 6 ; 44 ± 5	-28 ± 6 ; -74 ± 6 ; 41 ± 5
Motor regions			
Precentral gyrus	4/6	-46 ± 5 ; -4 ± 6 ; 48 ± 10	-44 ± 7 ; -3 ± 7 ; 41 ± 8
Med. frontal lobe (SMA)	6	-2 ± 3 ; 6 ± 10 ; 54 ± 5	-2 ± 2 ; 11 ± 7 ; 54 ± 5

Coordinates were calculated in the Talairach space for each of the subdivisions on the basis of individual response location. The reported coordinates suggest that some regions displayed slight spatial differences.

lowed for the assessment of variability between the two tasks (inter-session). The by-region analysis of the frequency of occurrence presented in Table II confirmed the predominant involvement of frontal areas in both tasks.

The inferior frontal gyrus (IFG)

Corresponding to Brodmann areas 44/45/47 or to Broca's area, the IFG was activated in almost all subjects during the rhyme (except for three) and the semantic task (except for one, see Table II). However, despite its high occurrence in both tasks, this region presented a pronounced variability across subjects as attested by a relatively high variance of localization (see Table I).

The prefrontal cortex (PFC)

When considered globally, the PFC, which essentially covers Brodmann areas 9/46/44 in the middle frontal gyrus, was robustly and frequently activated in both tasks (Table II). The subdivision of this region into the mid-dorsolateral prefrontal cortex (MDPFC, corresponding to BA 46/9), and the posterior prefrontal cortex (PPFC, corresponding to BA 9/44), as previously suggested [Petrides et al., 1993], revealed a high inter-individual variability within each task. In addition, the MDPFC tended to be more frequently activated than the PPFC in the rhyme task, while a reversed tendency was observed in the semantic task.

The temporal gyrus

The most consistent activations found in the temporal lobe involved Brodmann areas 21/22/42, which are thought to cover Wernicke's area. This region was almost equally activated in the rhyme and in semantic task (respectively, 19/26 and 20/26 subjects). The distinction within this region be-

tween the superior (STG, corresponding to BA 22/42) and the middle temporal gyrus (MTG, corresponding to BA 21/22) again showed a large disparity between subjects. In both tasks, the STG was shown to be more frequently activated than the MTG. It is worth noting that the posterior part of the middle temporal gyrus (BA 39/21) was activated in four subjects in the rhyme task and in five subjects in the semantic task. However, this activation was not evident in the averaged map and accordingly was not considered in further analysis.

Occipito-parietal region

This region included the inferior parietal lobule (IPL, BA 39/40) and the junction of the superior parietal lobule/the superior occipital gyrus (SPL, BA 19/7). Globally, the activation in these areas was observed more frequently in the rhyme than the semantic task (see Table II).

Motor regions

Motor regions were as frequently activated in the rhyme as in the semantic task. In both tasks, the activations concerned both the pre-central gyrus (PCG, BA 4/6) and the medial frontal gyrus (BA 6, SMA) although the frequency of responses was globally higher in the pre-central than in the medial frontal gyrus (Table II).

Combined Frequency Analysis

This analysis sought to examine to what extent a given region/regional subdivision could be found in both tasks in the same subject and how often a given region/regional subdivision could be activated in either one or the other or both tasks. Concerning the five major cortical regions, Figure 3A shows that they were activated in almost all subjects

Figure 2.

A: Projection of the mean coordinates of the activated areas (from Table I) on the Talairach space, according to the *y* (horizontal) and *z* (vertical) axis. Coordinates for the rhyme task (closed circles) and the semantic task (open triangles) are shown. **B:** Display of the Euclidean distance computed between mean locations for each activated subdivision in the rhyme and the semantic task. It is notable that the highest overlapping was observed in the STG and that the largest distances concerned the inferior parietal lobule (IPL).

(≥ 24 ; Fig. 3A, white histograms) when considering the two tasks together. When considering the number of subjects that activated the same region in both tasks, the frequency decreases considerably in the temporo-posterior areas (Fig. 3A, dark histograms). A similar analysis in the regional subdivisions revealed that, when considering the two tasks together, the most frequently activated areas were IFG, STG and PCG (26, 21, and 23 subjects, respectively; Fig. 3B, white histograms). However, when considering the number of subjects that activated the same subdivision in both tasks, it can again be noticed that the frequency decreases significantly in almost all subdivisions (except in the IFG; Fig. 3B, dark histograms).

Left Hemisphere Dominance

The laterality indices (LIs) illustrated in Figure 4A,B for the rhyme and semantic tasks indicate that both tasks have a highly LH lateralizing power. However, as shown in Figure 4C, a slight but significant difference was observed in favour of the semantic task (0.66 ± 0.27 and 0.76 ± 0.19 in the rhyme and in the semantic task, respectively, $t = -2.16$; $P < 0.04$; $df = 25$). In addition, a higher variability was observed in the rhyme compared to the semantic task.

Given the fact that the LI could be influenced by the fixed statistical threshold ($P < 0.005$) used in our study, we quantified this index for both tasks at different thresholds [see Nagata et al., 2001]. Figure 5 displays the evolution of the individual LIs as a function of the threshold. This illustration shows that the statistical threshold used in our analysis ($P < 0.005$, corresponding to $-\log_{10}(p) = 2.3$) is in the middle of the linear domain dependence between LI and $-\log_{10}(p)$, and accordingly skips the possible saturation of the LI (LI near to 1.0) for high thresholds and the inclination of the LI (LI near to 0.0) for low thresholds.

Frontal Versus Posterior Left Hemisphere Dominance

The frontal dominance index (FDI) was computed in order to determine to what extent LH frontal responses were dominant in each subject and task. This analysis showed significantly lower FDIs in the rhyme (mean = 0.09 ± 0.39) than in the semantic task (mean = 0.29 ± 0.28 , $t = -3.02$; $P < 0.006$; $df = 25$, see Fig. 6B,C). Once again, the rhyme task showed a higher variability than the semantic task as attested by the higher FDI variance and by the number of observations with negative FDI values.

Right Hemisphere Responses

Although almost all subjects showed LH dominance for the two tasks, some subjects manifested additional RH responses. In the rhyme task, the activations were found mainly in the right temporal gyrus in four subjects but also in the parietal lobule and other regions including the cuneus/lingual gyrus (BA 18/31) and the cingular gyrus in three subjects. In the semantic task, the most consistent activations were found in the right inferior frontal gyrus (BA 44/45) in four subjects and in the superior frontal gyrus (BA 8) in two subjects.

DISCUSSION

In this study, we used two language tasks in order to assess the variability of activation of language areas in healthy right-handed subjects. The rhyme detection task and the semantic categorization task used here have, in previous language studies, been shown to provide robust LH activation [Baciu et al., 2001; Billingsley et al., 2001; Kareken et al., 2000; Khateb et al., 1999; Lurito et al., 2000; Pugh et al., 1996; Seghier et al., 2001; Shaywitz et al., 1995a,b].

Performance analysis indicated that both tasks were successfully carried out in the scanner. In terms of task

TABLE II. The five major cortical regions, their subdivisions, and the corresponding Brodmann areas with the frequency of activation in each major cortical region and each regional subdivision

Regions/subdivisions	Brodmann area	f Rhyme (n)	f Semantic (n)
Inferior frontal gyrus	—	23	25
Broca area	44/45/47	23	25
Prefrontal cortex	—	24	25
Mid-dorsolateral prefrontal cortex	46/9	16	16
Post. prefrontal cortex	9/44	13	19
Temporal gyrus	—	19	20
Sup. temporal gyrus	22/42	15	17
Med. temporal gyrus	21/22	7	10
Occipito-parietal region	—	20	16
Inf. parietal lob.	39/40	13	8
Sup. parietal lob./Sup. occip. gyrus	7/19	14	12
Motor regions	—	20	19
Precentral gyrus	4/6	16	16
Med. frontal lobe (SMA)	6	12	12

This analysis confirms the predominant activation of frontal areas.

difficulty, no difference was observed between the tasks. Between conditions analysis of accuracy however, showed that the control conditions in both tasks (perceptual categorization of meaningless visual stimuli) induced a higher rate of correct responses than the activation conditions (rhyme detection and semantic categorization). Given the fact that our activation analysis always contrasted the activation versus the control condition, this difference in terms of accuracy cannot, in principle, influence the activation results.

In terms of activation, both tasks predominantly recruited LH frontal regions. In addition, significant activations were frequently observed in temporal, occipito-parietal, and motor areas. The analysis of individual activation maps allowed the identification in both tasks of nine cortical subdivisions distributed in five cortical areas. These regions correspond to areas repeatedly implicated in different language tasks in previous language investigations, including phonologic, semantic, and syntactic components [Friederici et al., 2000; Fujimaki et al., 1999; Keller et al., 2001; Kuperberg et al., 2000; Luke et al., 2002; Poldrack et al., 1999]. Although the rhyme detection (phonologic) and the semantic task globally involved the same brain areas, some differences (spatial/and or intensity) could be observed between the two tasks. These differences are separately commented on for each region involved.

Left Hemisphere and Frontal Dominance

The dominance of the LH in language production and comprehension tasks has been demonstrated in multiple previous imaging studies [Binder et al., 1996; Desmond et al., 1995; Leblanc et al., 1992; Springer et al., 1999]. This dominance, strongly observed in healthy, right-handed subjects [Frost et al., 1999; Knecht et al., 2000a; Vikingstad et al.,

2000], has also been found in left-handed and ambidextrous people [Pujol et al., 1999; Szaflarski et al., 2002]. In accordance with previous observations [Baciu et al., 2001; Billingsley et al., 2001; Kareken et al., 2000; Lurito et al., 2000; Pugh et al., 1996; Shaywitz et al., 1995a], LH dominance was observed in both the rhyme detection and the semantic categorization task. This observation at the group level was confirmed by individual LI measurements. These LIs, computed first at a fixed ($P < 0.005$) threshold, could be increased (i.e., higher lateralizing power) with higher statistical threshold as attested by the analysis of LI as a function of the statistical threshold [Nagata et al., 2001]. Concerning the rhyme task, this finding is supported by other studies showing strongly lateralized responses within the language-dominant LH for phonological processing [Démonet et al., 1994; Ramsey et al., 2001; Shaywitz et al., 1995a,b]. With regard to the semantic task, our findings differ from others suggesting that semantic judgment tasks induce weak laterality indices and high variability [Ramsey et al., 2001]. Concerning the capacity of these tasks to also detect RH activations in subjects with atypical language representation, we observed here, in line with other studies investigating right-handed healthy subjects [Springer et al., 1999], a bilateral language representation in only 2 of 26 subjects (~8%, shortcut at mean LI -2 SD; see Fig. 4), with no subject displaying exclusive RH dominance. In a previous report, we could observe an exclusive RH activation in an ambidextrous patient in whom language representation in the RH was supported by aphasic symptoms prior to, as well as after, neurosurgery [Seghier et al., 2001]. In a more recent report, a bilateral pattern of activation was observed during both tasks in a patient who transiently suffered from a crossed aphasia due to a right frontal meningioma [Khateb et al., 2004]. These findings indicate that these tasks are sensitive for detecting

Figure 3.

Combined frequency analysis, which shows to what extent a given region was found in both tasks in the same subject (dark gray bars) and to what extent the same region could be activated in either the rhyme or in the semantic or in the two tasks (white bars). **A:** Combined frequency analysis when considering the five major cortical regions. **B:** The same analysis when separately considering all 9 cortical subdivisions within the five regions. The analysis in the five major regions showed that all regions could reach a high probability of activation when considering the two tasks together (A). The same analysis in the regional subdivisions revealed that, when considering the two tasks together, the most frequently activated area was the IFG, followed by the STG and the PCG (B).

atypical language representation (some degree of bilateral representation or exclusive RH dominance) when language is not dominantly under the control of the LH.

Concerning the differences between the two tasks, our results showed that semantic categorization induced slightly more LH-lateralized responses than the rhyme detection task. In line with these observations, Lehericy et al. [2000] have suggested that the processing of semantic components in language tasks is a suitable tool to assess hemispheric dominance. In their study, the high LIs computed during

Figure 4.

A,B: Frequency of the laterality index (LI) of all subjects calculated in the rhyme (A) and the semantic task (B). These graphs show that both tasks have a highly LH lateralising power. However, a large inter-individual variability could be observed in both tasks. C: Mean (± 1.96 SEM and 1.96 SD) LI was significantly lower in the rhyme than in the semantic task and showed a larger variability.

Figure 5.

A,B: Individual laterality indices as a function of the statistical threshold in the rhyme detection (A) and the semantic categorization (B) task. The fixed statistical threshold ($P < 0.005$, $-\log_{10}(p) = 2.3$) is indicated by arrows on the graphs.

semantic fluency tasks correlated with the dominance index assessed by the Wada test.

Some previous studies have proposed that strong LH lateralization indexes were obtained in tasks implicating preferentially frontal regions [e.g., Lehericy et al., 2000; Spreer et al., 2002]. The analysis of FDI in an attempt to verify this assumption suggested that the differences observed in terms of LIs might be explained by a stronger

frontal activity in the semantic as compared to the phonologic task. Actually, we observed higher FDIs in the categorization than in the rhyme task. In addition, the voxel-by-voxel analysis comparing directly the strength of activation in both tasks revealed that voxels differentiating semantic from phonologic task were found in frontal regions while voxels differentiating phonologic from semantic task were found in more posterior regions. Although no Wada tests were conducted during this study, our results, together with other observations indicating that frontal activation asymmetry is more strongly correlated (than the temporal activation asymmetry [Binder et al., 1996; Desmond et al., 1995]) with the lateralization index of the Wada test [Lehericy et al., 2000; Spreer et al., 2002], suggest that the semantic categorization task might constitute a good tool for assessing language lateralization.

The Inferior Frontal Gyrus

Ever since Broca's observations, the role of the inferior frontal cortex (Broca's area), has repeatedly and consistently been recognized as the core for the planning and execution of speech. Moreover, Broca's area has been proposed to participate in various cognitive functions, including phonological [Zatorre et al., 1992], semantic [Roskies et al., 2001], and syntactic processing [Embick et al., 2000]. Within the IFG, several studies suggested that: semantic processing implies its antero-ventral part (BA 47); phonological processing involves its antero-dorsal part (BA 44/45); and syntactic processes recruit its postero-dorsal part (BA 44) [Dapretto and Bookheimer, 1999; Fiez, 1997; Friederici et al., 2000; Paulesu et al., 1997; Poldrack et al., 1999].

In line with previous observations [Billingsley et al., 2001; Klein et al., 1995; Pugh et al., 1996], no significant differences in terms of frequency of occurrence were detected in this study in the IFG between the phonological and semantic tasks. The fact that the IFG has been shown as the most frequently implicated area in both tasks demonstrates the reliability of IFG activation in our paradigm and indicates that it can be uncovered, with high probability, in healthy subjects even when using only one task. Combined frequency analysis showed that this probability could reach 100% when considering the two tasks together. A highly reliable IFG activation was previously reported during a verb generation task [Xiong et al. 2000] and semantic encoding tasks [Hund-Georgiadis et al., 2001].

Our spatial analysis indicated a relatively high variance in terms of x , y , z coordinates, which is in line with previous observations for this area [Xiong et al., 2000; Zilles et al., 1997]. In addition, it showed that a small distance separated the foci of activation in the IFG between the two tasks. The semantic task showed a slightly more infero-anterior mean activation than the rhyme task, which was also evidenced by the voxel-by-voxel analysis across subjects Z-score maps. This observation corroborates other findings suggesting the implication of more dorsal parts of the IFG during phonological tasks and of antero-ventral parts during semantic

Figure 6.

A,B: Frontal dominance index (FDI) of all subjects in the rhyme (A) and the semantic task (B). The FDI, based on the total number of significantly activated pixels in the LH only, was computed to determine to what extent frontal responses were dominant in each subject and task.

tasks [Fiez, 1997; McDermott et al., 2003; Poldrack et al., 1999].

The Prefrontal Cortex

The prefrontal cortex, a large region extending within the middle frontal gyrus, can be considered a crossroads for different tasks and cognitive functions [Miller, 2000]. In language studies, activation in the prefrontal cortex has been observed in various tasks including word generation, semantic categorization of words and pictures, and semantic fluency tasks [Gabrieli et al., 1998; Kapur et al., 1994; Lehericy et al., 2000]. On the basis of experiments on working memory, Petrides et al. [1993] dissociated mid-dorsolateral (MDPFC) from posterior prefrontal cortex (PPFC). Using such subdivisions in our analysis, we first observed that the MDPFC showed a comparable frequency of activation in the two tasks. In contrast, the frequency of activation in the PPFC was slightly higher in the semantic than in the rhyme task. A difference in this prefrontal region in favour of the semantic task was also observed in the voxel-by-voxel analysis. Moreover, the fact that the mid-dorsolateral prefrontal cortex was more frequently activated than the posterior prefrontal cortex during the rhyme detection task, while the inverse was true for the semantic task, may support the hypothesis of a certain functional segregation in this area [e.g., Dobbins et al., 2002; Sharp et al., 2004]. Considering the prefrontal cortex as a whole showed that, in line with previous reports [Billingsley et al., 2001; Lurito et al., 2000], activation in this region was highly reliable in both the rhyme and semantic task. This finding indicates that the probability in locating this region in healthy subjects, even when using only a single language task, is very high. In addition, the variance of activation location in the prefrontal

regions was the smallest compared to the other activated foci, suggesting a relatively low inter-individual variability.

The Temporal Gyrus

With Wernicke's area situated in the posterior superior temporal gyrus (22 BA) [Papathanassiou et al., 2000], the temporal gyrus has repeatedly been shown to be involved in language comprehension and production [Burton et al., 2001; Démonet et al., 1992, 1994; Naeser et al., 1987; Rumsey et al., 1997; Zatorre et al., 1992]. Here, the observed activation of the temporal gyrus in the two tasks is consistent with many previous studies. For instance, activation in the superior temporal gyrus has already been observed in rhyme detection and semantic judgment tasks [Billingsley et al., 2001; Lurito et al., 2000; Pugh et al., 1996; Shaywitz et al., 1995b].

We observed that our tasks involved both the middle and superior temporal gyrus. In a similar way, the two areas have been found in a semantic decision task [Binder et al., 1997], in rhyme and categorical tasks [Billingsley et al., 2001] and in sentence processing tasks [Kuperberg et al., 2000; Stippich et al., 2003]. In accordance with other observations, and despite the overlapping in the location coordinates of the STG in the two tasks, the voxel-by-voxel analysis suggested a greater involvement of the posterior STG in the phonologic compared to the semantic task [Billingsley et al., 2001]. Concerning the spatial variability between subjects, temporal regions presented a high location variance as already observed in other language studies [Burton et al., 2001; Xiong et al., 2000].

Globally, the temporal regions were as frequently activated by the semantic as by the rhyme task. Within the

temporal gyrus, our results indicated that the STG was more frequently activated in both tasks than MTG. This low frequency in the MTG may be explained by the use of the visual presentation as suggested by previous observations showing that the temporal areas were more recruited with auditory than with visual presentations of words [Chee et al., 1999]. Although the frequency of activation in the temporal gyrus was relatively weak in both tasks (~75%), the combined analysis of frequency showed that this frequency could reach 92% when using two tasks. In accordance with these findings, other studies have also observed weak, or even a lack of, activation in this area in language tasks [Devlin et al., 2000; Kang et al., 1999; Schlösser et al., 1998; Stippich et al., 2003]. Absence of activation in Wernicke's area has been attributed to the loss of fMRI signal in temporal regions [Devlin et al., 2000]. Noteworthy is the fact that other studies have shown additional activation in the inferior temporal gyrus and the fusiform gyrus (BA 37) in rhyming tasks [Kareken et al., 2000; Lurito et al., 2000] but these two regions have not been explored in our study due to technical limitations.

Occipito-Parietal Regions

The inferior parietal lobe, generally subdivided into the supramarginal gyrus (BA 40) and the angular gyrus (BA 39), has been involved in various language tasks. In particular, the supramarginal gyrus has specifically been implicated in phonological processes [Démonet et al., 1994; Paulesu et al., 1993], while the angular gyrus has been involved in semantic processing [Binder et al., 1997; Price, 2000].

Activation in the inferior parietal lobule has also been observed during rhyme detection and categorical judgment tasks [Billingsley et al., 2001; Lurito et al., 2000]. In our study, occipito-parietal regions were activated with a relatively moderate frequency. Globally, these regions were activated more frequently in the rhyme than the semantic task. In concurrence with previous observations, spatial analysis showed that the activation of the inferior parietal lobule (BA 39/40) was more anterior and inferior during the phonologic than the semantic task [Mazoyer et al., 1993; Zatorre et al., 1992], a fact also confirmed by the intensity/spatial (voxel-by-voxel) analysis. It should also be noted that the occipito-parietal regions presented a higher location variance during the phonologic than the semantic task. If considered with the fact that the phonological task showed a slightly higher frequency of activation in these regions than the semantic task, these observations would suggest that a certain functional segregation might exist in occipito-parietal regions in relation to phonological and semantic processing. Concerning between-subjects differences, both tasks (particularly the semantic) exhibited a relatively high degree of inter-individual variability. The combined analysis showed, however, that frequency of activation of these regions can significantly be increased when considering the

two tasks (92%). It should be pointed out that, if we consider the subjects who activated occipito-parietal regions in both tasks (12/26 subjects), the frequency of activation decreased, reflecting considerable within-subjects variability.

Motor Areas

Activation in motor regions has been observed in various previous language studies [Chee et al., 1999; Karbe et al., 1998; Lehericy et al., 2000; Paulesu et al., 1993], and has often been associated with phonological and articulatory encoding processes. The pre-central gyrus and SMA were, for instance, activated during verb generation [Papathanassiou et al., 2000; Xiong et al., 2000], and reading tasks [Fiez and Petersen, 1998; Turkeltaub et al., 2002]. In semantic fluency and word repetition tasks, the SMA has been found more frequently activated than the temporo-parietal regions [Burton et al., 2001; Lehericy et al., 2000]. In our study, the SMA and the pre-central gyrus were activated as frequently in the rhyme as in the semantic task. This finding contrasts with previous investigations reporting the absence of activation in the SMA or the pre-motor cortex during rhyme detection [Billingsley et al., 2001; Lurito et al., 2000]. In both tasks, activation in left motor regions could not be attributed to right-hand button presses used in our paradigms. In both conditions (control and activation), motor responses constituted a constant since the same rate of motor responses was required and this equally in both tasks. Accordingly, the pure motor responses are not visible in our contrasts "activation-control." Moreover, a recent study showed that the responding hand had no effect on the activation pattern in language paradigms [Hund-Georgiadis et al., 2001]. Furthermore, involvement of right motor regions during the same tasks has already been documented in patients with atypical language representation [Khateb et al., 2004; Seghier et al., 2001].

As already observed by Xiong et al. [2000], the spatial analysis indicated a higher variance in the z-axis in both tasks for the precentral cortex and a more variable location in the y-axis for the SMA. Unlike previous studies suggesting an unspecific role of motor regions (particularly the SMA) in language processing [Binder et al., 1997; Fujimaki et al., 1999], our voxel-by-voxel analysis showed that the SMA was more strongly implicated in the phonologic than in the semantic task, thus corroborating the predominant role of the SMA in phonologic processing [Chee et al., 1999; Paulesu et al., 1993]. In the two tasks, both the pre-central cortex and the SMA showed a high degree of inter-individual variability. Considering the two motor regions together increases the probability of activation in each task up to ~75%. This frequency contrasts with previous studies, particularly those using language production tasks, where the frequency of activation of motor areas is much higher [Xiong et al., 2000]. Finally, when considering the two tasks together, the probability to observe activation in these regions reaches ~92%, also indicating a large between-tasks variability.

Implications in the Investigation of Brain-Damaged Patients

In recent years, several studies attempted to correlate fMRI activations in language paradigms with the results of the Wada test in order to reduce its use in clinical practice [Binder et al., 1996; Lehericy et al., 2000; Rutten et al., 2002b; Woermann et al., 2003]. For instance, Binder et al. [1996] have shown a 95% correlation between fMRI measures and Wada tests. In patients with LH, RH, and mixed (both hemispheres) dominance, Rutten et al. [2002b] showed a high correlation between LIs in fMRI activation and Wada results in all subgroups. Finally, in a large group of 100 epileptic patients, Woermann et al. [2003] found 91% concordance between language dominance by fMRI with results of the Wada test. Although the majority of these studies indicates that fMRI activation indices might constitute a suitable tool for assessing language lateralization, a correlation could not be found between the two tests in some particular cases. In these patients, the discrepancy may be explained by certain patho-physiological changes that may result from the disturbed cerebral autoregulation [Rother et al., 2002; Shiino et al., 2003] or abnormal cerebral activities [Jayakar et al., 2002].

Before applying experimental paradigms to clinical practice, one must ensure having at hand a task that is validated and feasible (by the patients) and that provides robust and reliable fMRI responses. For assessing the robustness and reliability of responses, one should first determine inter-individual variability of fMRI activation and even the reproducibility of within-subjects activations. For this purpose, one should also minimize the different methodological sources of variability [Hund-Georgiadis et al., 2001]. In language studies more particularly, the tasks must be able to reveal consistent activations in classical LH language areas, but also to detect RH activations in subjects with atypical language representation. In this study, we validated our fast paradigms in a relatively large population of control subjects and showed, by the individual analysis, the extent of implication of each activated area. Our results pointed to the fact that frontal regions were the most dominantly activated, but also that when a combined analysis of frequency was performed almost all regions showed a high probability of occurrence. In previous reports, we could also show that our tasks were able to reveal either bilateral [Khateb et al., 2004] or exclusive RH activations [Seghier et al., 2001] in patients in whom RH activation correlated with aphasic symptoms. In the light of previous studies, we propose that the combination of the two tasks tested in this study may be used to determine language lateralization and to map the major language areas prior to neurosurgery.

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