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Auditory and visual stimuli in language mapping by functional MRI: Is it modality specific?

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ABSTRACT

Human language is a complex process that involves specialized subsystems with certain modularity of organization. Mapping of language processing is of interest because of its social importance and clinical applications. Therefore, the purpose of the present study was to assess language processing using auditory and visual stimuli to determine if both stimulus modalities were robust for language mapping. Moreover, language lateralization was evaluated. Seventeen right handed asymptomatic subjects, native Portuguese speakers, performed a word generation task cued either by visual or auditory stimulus. As expected, language representation was mainly observed in the left frontal gyrus, including Broca's area, left precentral and poscentral gyri, insula, and left superior temporal gyri, including Wernicke's area, for both stimulus modalities. Other regions were also observed: bilateral cingulate and fusiform gyri; left parahippocampal, supramarginal and lingual gyri; thalamus, left parietal lobe and primary visual cortex. Laterality indices and centroids of these regions were not modality specific. Therefore, both stimulus modalities in combination with a simple verbal fluency task were robust for language mapping, allowing their application in different groups of patients.

KEYWORDS: word generation, visual and auditory stimuli, hemispheric lateralization, language, functional MRI

INTRODUCTION

One of the most complex human functions is the capacity to associate symbols to their meanings, and express thoughts and emotions through language. Cerebral areas involved with this function are of particular interest, since language, beyond its social importance, has important clinical applications.

However, human language is not a single process, but rather involves specialized subsystems with certain modularity of organization. Although there is no single and consensual model to the language system, one widely accepted involves two fundamental structures: the anterior part of the frontal lobe - Broca's area [1], and posterior part of the superior temporal gyrus - Wernicke's area [2]. According to this model, expressive language function would be centered at Broca's area, while receptive language fields would be associated with Wernicke's area.

On the other hand, due to the increased availability of functional neuroimaging tools, capable of non-invasively studying certain aspects of human brain functions, other language models have been recently proposed. For instance, Price's model gives emphasis on semantic processing and highlights the involvement of additional regions

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to Broca's and Wernicke's area, such as the parietal angular gyrus and the anterior inferior temporal cortex [3]. Friederici's model supports that Broca's area is involved not only in processing language syntax as traditionally assumed, but also in oral sequences [4]. Another example is the word production model of Indefrey and Levelt, which considers that other brain areas are involved in language processing, such as the middle temporal gyrus, the inferior precentral and the inferior postcentral gyri [5].

Two recent reviews have investigated hundreds of studies of speech comprehension and production, and summarized the results in an anatomical model that indicates the location of language areas and their most consistent functions [6, 7]. Although many findings were shown to be reliable regarding language localization, the need to better understand brain pathways that integrate brain regions involved with the human language function is emphasized.

Besides the understanding of the language system, of utmost importance in the clinical practice is the determination of language hemispherical dominance. For most people, language processing is left lateralized [8-10]. The gold standard technique for determination of language dominance has been the Wada test, which is based on deactivation of language cortex with intracarotid anesthesia [11]. However, it is an invasive test that carries risks and discomforts, and it is not specific for regions and gyri, because it numbs most of the hemisphere [12, 13]. Furthermore, the Wada Test has mainly been performed on epileptic patients that can show atypical lateralization, precluding the assessment of language dominance in healthy brains [14, 15].

Some other techniques have been used for language lateralization and also localization. Although extremely useful, these methodologies are generally invasive (subdural grid stimulation mapping, intraoperative cortical stimulation mapping - ICSM), costly, and not widely available (positron emission tomography - PET, magnetoencephalography - MEG). Therefore, due to its non-invasiveness, availability and good spatial resolution [16, 17], functional magnetic resonance imaging (fMRI) has received attention as an alternative technique [18, 19].

Beyond listening, repeating, reading and object-naming, the word generation (WG) task has been widely used for language mapping; it requires word retrieval in response to a cue. Subjects must retrieve a word phonologically or semantically associated with a specific letter, a semantic category, or a word. Unlike the rest, word generation demands output phonology, verbal working memory, and lexical search systems. This task strongly activates the dominant inferior and dorso-lateral frontal lobe, including prefrontal and premotor areas [20, 21]. Previous studies have demonstrated that fMRI, WG task and auditory stimulus robustly localize Broca's area, and can be used to assess noninvasively language lateralization in different groups of healthy subjects and also preoperative patients, including children [22-25].

Although auditory stimulus is widely used, it is of interest to study language representation using different stimulus modalities in combination with a simple task, such as word generation, to be used with different groups, such as deaf subjects or aphasic patients, for example. Therefore, the purpose of the present study was to assess language processing during a word generation task using auditory and visual stimuli to determine if both stimulus modalities are robust for language mapping and to identify eventual stimulus modality specificities.

MATERIALS AND METHODS

Subjects

Seventeen asymptomatic volunteers (10 men and 7 women; mean age 26.8 years, range 17 to 48 years) participated in this study. The Edinburgh Handedness Scale was used to measure lateralization quotients [26]. They were native Portuguese speakers, and had no history of neurological or psychiatric diseases. Two were excluded from analyses due to uncorrectable amounts of head movement, leaving 15 right-handed participants in the final dataset (8 men, 7 women). The study was approved by the Ethics Committee of the University of Sao Paulo. Informed consent was obtained in accordance with their guidelines.

Paradigm

Before entering the scanner, all subjects were provided with detailed instructions. Subjects were instructed to generate as many words as possible beginning with the letter presented either by visual or auditory stimulus, which were conducted in two different runs. All subjects performed both tasks in the same session. To minimize head movement artifacts, subjects were asked to keep their mouths closed and to perform the tasks silently.

The protocol consisted of five intervals of word generation (27.5 seconds each), intercalated by six intervals of rest (27.5 seconds each). During rest, volunteers were instructed to stop language production and to think on a white wall.

For visual stimulus (VS), letters were presented via a video projector and a screen was placed near the subject's feet. Letters were seen through a mirror attached to the MRI head coil. For auditory stimulus (AS), instructions were recorded in a CD, synchronized to the image acquisition, and were listened through a headphone system. Prior to the scans, a test was performed to certify that the subjects could listen and see the letters.

MRI acquisition

MRI was acquired in a 1.5T scanner (Magneton Vision, Siemens). Functional imaging consisted of 16 axial slice series, covering from brain most superior regions to the cerebellum, using fast EPI-BOLD fMRI sequences with: TR = 3000 ms; TE = 118 ms; flip angle = 90°; FOV = 210 mm; slice thickness = 4 mm, no gap. For overlay purposes, a set of high-resolution T1-weighted images were acquired with: TR = 9.7 ms; TE = 4.0 ms; matrix size = 256 x 256; flip angle = 12º; FOV = 256 mm; slice thickness = 1 mm, using a Gradient Recalled Echo (GRE), MPR sequence.

Data analysis

Data analyses were performed with BrainVoyager^{QX} software (Brain Innovation, Maastricht, The Netherlands). Preprocessing included motion correction, temporal correction between slices, temporal filtering using a high pass filter of 3 cycles/sec and a spatial filtering with a Gaussian kernel (full width at half maximum = 4 mm).

Statistical analysis was conducted with the General Linear Model (GLM), and only clusters of more than fifty statistically significant ($p<0.001$) voxels were considered. Individual maps were normalized to the Talairach space in order to obtain average maps and perform inter-subject comparisons.

Averaged maps were obtained for each stimulus modality and, then, a conjunction analysis was performed to identify common activated areas for both modalities [27]. Talairach coordinates (x, y, z) were also obtained for each cluster to assess spatial differences between stimulus modalities. A parametric one-way ANOVA with Bonferroni's multiple comparison test ($p < 0.05$, corrected for 3 tests and 18 ROIs) was used to check for differences.

To assess the variability of activation maps between subjects, the frequency of activation (FA) of each region, which refers to the number of individuals that show activation in such regions, was determined analyzing the individual maps [28].

Additionally, the laterality index (LI) was calculated for each subject and for the average maps of each stimulus modality, using the total number of significantly activated voxels in the left (V_L) and in the right (V_R) hemispheres, according to:

$$LI = \left(\frac{V_L - V_R}{V_L + V_R}\right).$$

LI varied from +1 (left hemisphere dominance) to -1 (right hemisphere dominance). When $|LI| < 0.20$, language dominance was classified as bilateral [9]. LI was also calculated for each activated region, computing the total numbers of significantly activated pixels in specific regions of interest (ROI) of both hemispheres.

RESULTS

Robust BOLD signal change was observed in average maps for a word generation task cued by both auditory and visual stimuli (Figure 1). A conjunction analysis allowed the identification of brain areas that showed BOLD signal change for both stimulus modalities (Figure 2): cingulate gyrus; inferior frontal gyrus (Broca's area); medial, middle and superior frontal gyri; insula; parahippocampal gyrus; postcentral and precentral gyri; superior and inferior parietal lobules, including supramarginal gyrus; thalamus; lingual gyrus; and superior temporal gyrus.

BOLD signal change was also observed, in both hemispheres, in the primary visual cortex and fusiform gyrus, but only for VS. These regions

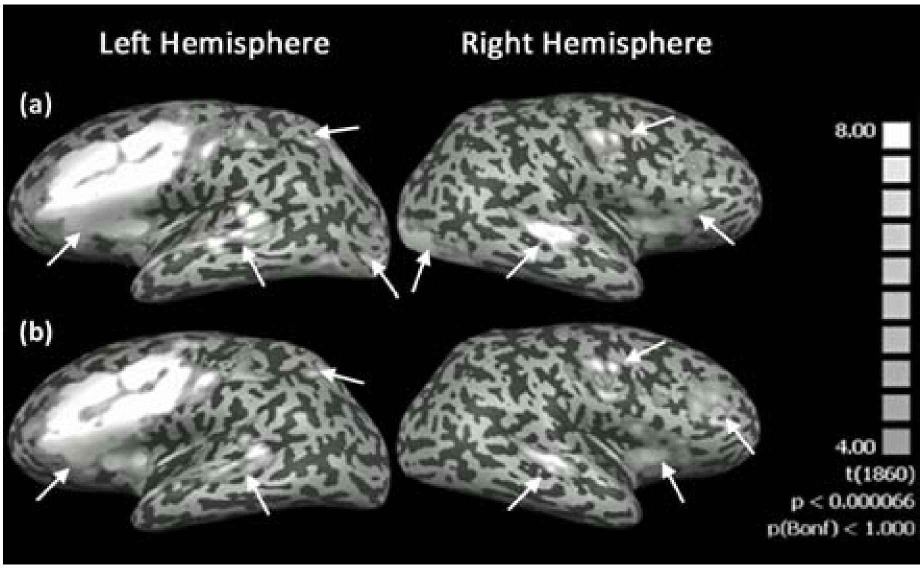

Figure 1. Average maps of activated areas (arrows) for (a) visual and (b) auditory stimuli, for a word generation task.

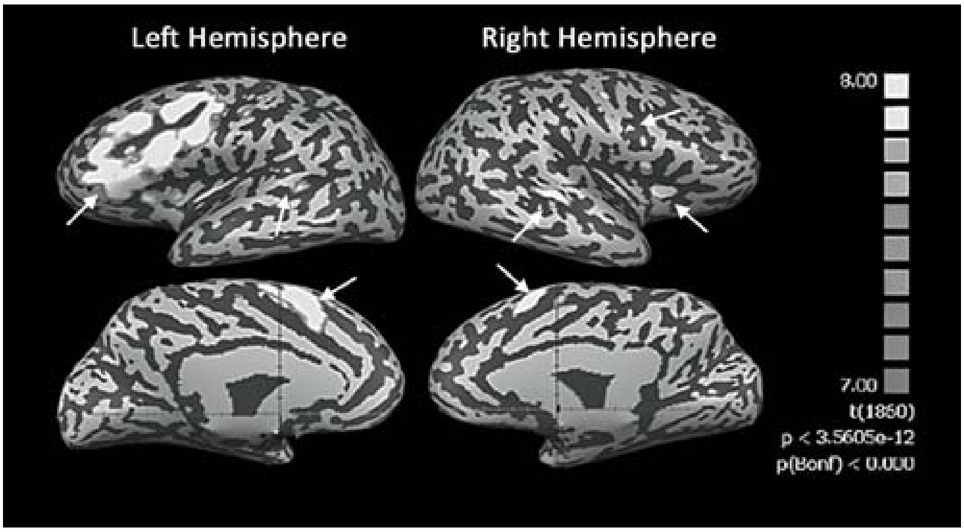

Figure 2. Average map of brain areas that showed BOLD signal change (arrows) for both stimulus modalities, during a word generation task.

can be observed in the average map that shows areas obtained only for VS, that is, using the contrast Visual > Auditory (Figure 3a). On the other hand, for Auditory > Visual, the average map showed BOLD signal change in the cingulate gyrus, medial frontal gyrus and inferior parietal lobule (Figure 3b). These regions were also observed for VS; however, Figure 3b shows that AS activates cingulate and medial frontal gyri more anteriorly and inferior parietal lobule more posteriorly.

Regardless the stimulus, in all subjects, BOLD signal change was observed in the frontal gyrus, insula and superior temporal gyrus (Table 1), confirming the predominant involvement of frontal regions, including Broca's area, and Wernicke's area in word generation tasks. Other

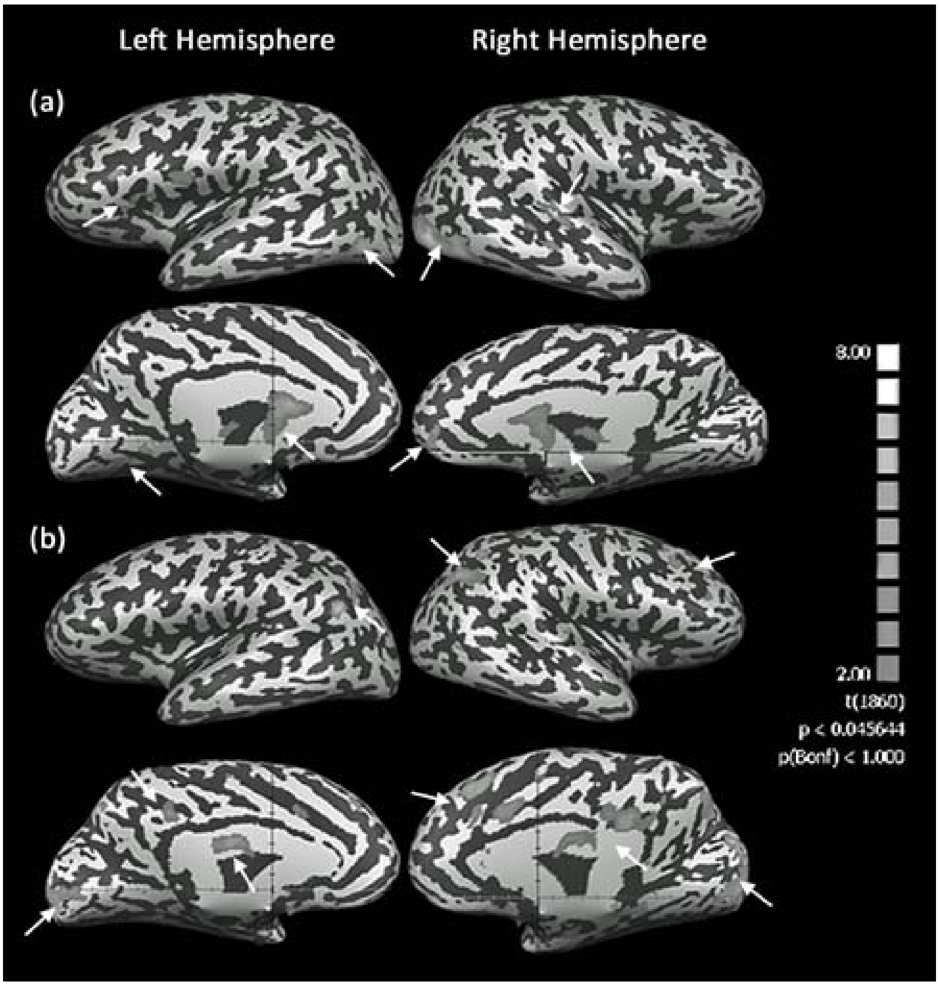

Figure 3. Average maps of BOLD signal change showing brain regions (arrows) obtained only for (a) visual (Visual > Auditory) and (b) auditory stimuli (Auditory > Visual), for a word generation task.

areas were activated in less than ten subjects (thalamus, anterior cingulate, parahippocampal and supramarginal gyri), but BOLD signal changes were still statistically significant in average maps, where data from all subjects were considered.

Language laterality was also calculated. Considering all significant voxels in each hemisphere, LI values were 0.27 and 0.25, for AS and VS, respectively. It should be noted that this strategy of LI calculation has decreased specificity, since all significant activated clusters are computed regardless the direct involvement of the region in language processing, such as the visual cortex. Therefore, LI were calculated for different regions of interest (Table 1). Although most of the regions presented left dominance, the cingulate and fusiform gyri, insula, thalamus, and primary visual cortex indicated bilateral involvement.

Table 2 shows the mean Talairach coordinates of the activated regions, in the left hemisphere, enabling the evaluation of spatial differences between AS and VS. All significantly activated areas were centered in similar regions of the brain when comparing AS and VS.

DISCUSSION

In the present study, a word generation task was performed by healthy subjects after letters being presented using two different stimulus modalities, auditory and visual, in order to assess the activation variability of language areas. The regional distribution

Table 1. Mean laterality indices (LI) and frequency of activation (FA) of all activated regions, and the corresponding Brodmann areas, for the word generation task, during auditory and visual stimuli.

		LI			FA (n)	
Regions of Interest	**Brodmann Area**	**Auditory**	**Visual**	**AV***	**Auditory**	**Visual**
Anterior Cingulate Gyrus	10 / 24 / 32	0.76	0.75	1.00	7	5
Cingulate Gyrus	23 / 24 / 31 / 32	0.01	0.19	0.17	15	14
Frontal gyrus						
Inferior frontal gyrus (Broca's area)	44 / 45 / 47	0.85	0.85	0.91	15	15
Medial frontal gyrus	6 / 8	0.30	0.32	0.42	15	15
Middle frontal gyrus	6 / 8 / 9 / 10 / 46	0.98	0.97	1.00	15	15
Superior frontal gyrus	6 / 8 / 9	0.37	0.36	0.37	15	15
Fusiform Gyrus	37	-	0.12	-	8	15
Insula	13	0.08	-0.09	-0.03	15	15
Parahippocampal Gyrus		0.44	0.30	0.55	10	8
Parietal Lobule						
Superior Parietal Lobule	7	1.00	1.00	1.00	12	10
Inferior Parietal Lobule	7 / 40	0.72	0.78	0.94	15	14
Postcentral Gyrus	1 / 2 / 3 / 4 / 43	0.56	0.56	0.72	12	14
Precentral Gyrus	4 / 6	0.43	0.42	0.57	15	14
Superior Temporal Gyrus	21 / 22 / 38	0.38	0.31	0.44	15	15
Supramarginal Gyrus	40	0.85	1.00	1.00	8	9
Thalamus		0.16	0.16	0.18	6	7
Visual Cortex						
Primary Visual Cortex	17	-	-0.19	-	4	13
Lingual gyrus	18 / 19	0.17	0.24	0.41	7	13

*Regions shared by both stimuli obtained by conjunction analysis.

of modality-independent phonological processing found herein was in accordance with previous reports [6, 7, 29, 30].

As expected for word generation tasks, language processing was mainly represented in the frontal cortex of the left hemisphere. The left inferior frontal cortex, which includes Broca's area, has a role in phonological production of words [5, 31-33], and is also involved in planning and execution of speech, assembling syllables, within and between words [34, 35]. Robust activation was also observed in left middle, medial and superior frontal cortices, and pre-central and post-central gyri. These areas include the pre-motor and supplementary motor cortices involved in phonological, semantic and articulatory encoding processes [32, 35].

Representation of language processing was also present in the insula, cingulate gyrus, and left superior temporal gyrus. The insula has a functional role conducting the articulatory planning of speech performed by Broca's area [3], mainly during automatic speech production [7]. It is known that permanent speech production difficulties are observed when damage is present not only in frontal lobe, but also extends to the insula and parietal regions of the patient [36].

Table 2. Mean (± standard deviation) x, y and z Talairach coordinates of activated regions, and the corresponding Brodmann areas, for the word generation task, during auditory and visual stimuli.

	Talairach Coordinates								
	Auditory			**Visual**			**AV***		
Regions of Interest	**x**	**y**	**z**	**x**	**y**	**z**	**x**	**y**	**Z**
Anterior Cingulate Gyrus	-7 ± 4	26 ± 4	24 ± 1	-11 ± 4	31 ± 10	15 ± 13	-8 ± 1	24 ± 3	24 ± 1
Cingulate Gyrus	-6 ± 4	10 ± 12	35 ± 6	-7 ± 5	7 ± 13	37 ± 6	-6 ± 3	10 ± 10	37 ± 6
Frontal gyrus									
Inferior frontal gyrus (Broca's area)	-47 ± 7	18 ± 10	11 ± 12	-47 ± 8	18 ± 10	18 ± 10	-48 ± 7	18 ± 10	12 ± 12
Medial frontal gyrus	-6 ± 4	7 ± 17	49 ± 9	-6 ± 4	5 ± 15	50 ± 10	-6 ± 3	4 ± 14	51 ± 8
Middle frontal gyrus	-38 ± 8	20 ± 19	34 ± 14	-39 ± 8	21 ± 19	32 ± 14	-40 ± 7	21 ± 18	32 ± 13
Superior frontal gyrus	-16 ± 13	25 ± 20	43 ± 17	-15 ± 13	22 ± 20	44 ± 17	-15 ± 14	22 ± 20	44 ± 16
Fusiform Gyrus	-	-	-	-36 ± 9	-61 ± 15	-14 ± 3	-	-	-
Insula	-38 ± 4	-2 ± 18	9 ± 8	-38 ± 4	3 ± 16	8 ± 8	-37 ± 4	7 ± 13	7 ± 7
Parahippocampal Gyrus	-24 ± 7	-25 ± 15	-10 ± 6	-24 ± 7	-26 ± 14	-10 ± 6	-24 ± 7	-24 ± 14	-10 ± 5
Parietal Lobule									
Superior Parietal Lobule	-27 ± 5	-63 ± 5	45 ± 2	-28 ± 5	-62 ± 6	45 ± 2	-28 ± 4	-64 ± 5	44 ± 1
Inferior Parietal Lobule	-46 ± 6	-41 ± 7	45 ± 6	-44 ± 6	-39 ± 8	43 ± 5	-45 ± 5	-40 ± 8	42 ± 6
Postcentral Gyrus	-49 ± 9	-20 ± 7	41 ± 1	-50 ± 9	-20 ± 6	41 ± 9	-51 ± 8	-18 ± 5	40 ± 10
Precentral Gyrus	-45 ± 9	-5 ± 11	38 ± 15	-45 ± 9	-5 ± 10	37 ± 15	-49 ± 5	-4 ± 10	37 ± 15
Superior Temporal Gyrus	-53 ± 7	-10 ± 17	1 ± 6	-53 ± 6	-9 ± 18	0 ± 7	-53 ± 5	-8 ± 19	1 ± 6
Supramarginal Gyrus	-42 ± 2	-42 ± 2	35 ± 1	-41 ± 2	-43 ± 2	36 ± 1	-42 ± 2	-42 ± 2	35 ± 1
Thalamus	-12 ± 5	-17 ± 6	9 ± 5	-13 ± 6	-17 ± 6	7 ± 4	-13 ± 4	-15 ± 4	8 ± 4
Visual Cortex									
Primary Visual Cortex	-	-	-	-31 ± 7	-83 ± 6	-5 ± 5	-	-	-
Lingual gyrus	-13 ± 7	-73 ± 10	-2 ± 5	-17 ± 5	-70 ± 9	-4 ± 4	-17 ± 6	-70 ± 10	-2 ± 5

*Regions shared by both stimuli obtained by conjunction analysis.

Moreover the cingulate gyrus has consistently being reported as an important area in language representation, in part possibly due to its involvement in emotion formation and processing, learning, and memory [21, 23, 34]. Moreover, the cingulate gyrus, mainly its anterior part, is associated with the subject's wish to participate and also with the suppression of inappropriate responses when there are multiple alternatives [6, 7]. Finally, the superior temporal gyrus, including Wernicke's area, is involved in the understanding of written and spoken language. Therefore, it is present in average maps obtained for both stimulus modalities, visual and auditory [37].

Moreover, the task used in the present study also requires verbal working memory, showed by the extensive representation in the prefrontal and parietal cortices, cingulated gyrus, insula and thalamus [38, 39]. Also, these areas are related with the inhibitory control involved in tasks silently performed [40].

However, the primary auditory cortex was not substantially represented in the maps, in contrast with previous studies using auditory stimulus [6, 7, 41]. The activation from auditory systems was minimized by verbally presenting a letter only once in each interval, that is, not repeating it during the word production.

On the other hand, for visual stimulus, the letter was left on the screen during word production. Then, to minimize activation of the primary visual cortex, during the baseline condition, a block with the same size and color of the letter was presented. Still, the visual association cortex was present in activation maps, probably due to the fact that visual language processing begins in some regions of the occipital cortex involved in identifying orthographic forms and in translating these forms into a phonological representation [32, 37].

Considering areas observed for both stimuli, the centroids of statistically significant clusters were not modality specific, as previously reported [42]. This overlap between verbal and visual language processing may be due to the fact that visually presented language is translated into phonological form at an early stage of processing. However, this result is in contrast with Michael *et al.* [43] who showed that activated regions are more anterior for auditory conditions than for visual conditions. But in that case, they used a sentence comprehension task that is more complex, and recruits other areas involved in high levels of language processing.

Language lateralization was also assessed in the present study. When considering the whole brain, the laterality results showed slight left dominance for both stimulus modalities. As previously reported, left dominance is expected for the majority of right-handed subjects [8-10]. However, as recently discussed [6], estimation of language lateralization on a region by region basis is required to understand the determinants of lateralization. Therefore, in the present study, this evaluation was performed and, for each assessed region, indices showed the same lateralization regardless the stimulus modality. Moreover, for most regions, language was left lateralized. Bilateral lateralization was observed for the cingulate gyrus, fusiform gyrus, insula, thalamus and primary visual cortex.

CONCLUSION

The present study demonstrated a protocol that can be easily implemented into clinical routine and be applied in several groups of patients. Since word generation is not a difficult task to be performed, it can be applied in aphasic patients, for example, to evaluate their rehabilitation therapy. Moreover, it also demonstrated that language function can be assessed with visual stimulus. Although auditory stimulus is widely used, visual is of interested in studies with deaf subjects or even in cases when the scanner noise makes it difficult to understand the auditory task.

ABBREVIATIONS

AS	-	Auditory Stimulus
BOLD	-	Blood Oxygenation Level Dependent
FA	-	Frequency of Activation
fMRI	-	Functional Magnetic Resonance Imaging
GLM	-	General Linear Model
ICSM	-	Intraoperative Cortical Stimulation Mapping
LI	-	Laterality Index
MEG	-	Magnetoencephalography
PET	-	Positron Emission Tomography
ROI	-	Region of Interest
VS	-	Visual Stimulus
WG	-	Word Generation

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