

**Research article**

## The Network of Brodmann's Area 22 in Lexico-semantic Processing: A Pooling-data Connectivity Study

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**Abstract: Background and Objective:** Modern neuroimaging has demonstrated that cognitive functions are based in networks of interconnected modules. The purpose of this paper was to analyze the connectivity of Brodmann's area (BA) 22 in lexico-semantic tasks. **Methods:** A connectivity fMRI co-activation study was performed by pooling data of lexico-semantic tasks in which BA22 (core of Wernicke's area) was reported. 283 subjects reported in 21 experiments were analyzed. Analysis of Likelihood Estimates of pooled data was utilized to generate the connectivity map; thresholds at  $p < 0.01$  were corrected for multiple comparisons with false discovery rate. Resulting images were co-registered into MNI standard space. **Results:** A network consisting of 13 clusters of activation was obtained. Main clusters were located in the left posterior temporal and left inferior frontal gyrus; in addition to these canonical areas, left insula, pre-supplementary motor area, left BA37, primary auditory areas and left occipital lobe were also involved. **Conclusions:** BA22-related networks involved in lexico-semantics processing were demonstrated utilizing a pooling-data connectivity study. Significance, interpretation and limitations of the results are discussed.

**Keywords:** Brodmann; semantic; language; connectivity; Wernicke; fMRI

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## 1. Introduction

The contribution of Brodmann's cortical parcelation to the understanding and description of brain functions has been of critical importance in the field of neuroscience. The attempt to link histological cortical differences to specific sensory, motor and cognitive skills sounds reasonable. However, modern neuroimaging techniques have demonstrated that each of these areas in which the cortex is subdivided, may be involved in different functions. Brodmann's area (BA) 22, for example, has been found to be not only involved in receptive language tasks, as core part of the Wernicke's area, but also participating in quite distinct tasks as processing of complex sounds [1], and deductive verbal reasoning [2]. Lexical-semantic analysis, that is, the decoding of meaning from primary auditory or visual sensory input, is one important function of BA22 [3,4].

A large number of publications correlate brain function to networks; however, there is a paucity of articles examining the bases and theoretical background on this topic. Despite this lack, it is currently well accepted that cognition correlates to brain network configuration [5]. This means that any specific area (e.g., BA22) may connect with different modules, depending of the task, yielding specific network configurations from which arise distinct brain functions. Brain connectivity, the term referring to this view, may explain better complex cognitive, behavioral and neuropsychological phenomena than simple localization models.

Brain functional connectivity may be assessed by different methods. Perhaps the most popular currently is related to task-less fMRI or resting state fMRI. Fewer studies, instead, have explored brain connectivity related to tasks [6–8]. A recent described methodology that relies on pooled data analysis of coactivations found in task-related fMRI has also been described to depict brain functional networks. The method has been originally termed *Meta-Analytic Connectivity Model* (MACM) [9–11]. In the present study we utilize this method to describe Wernicke's area core network involved in semantics, more specifically in lexico-semantic analysis. We have preferred to term it "pooling-data connectivity study" to avoid confusion with the standard meta-analysis methodology which usually requires broader sources.

## 2. Materials and Methods

The data source for this pooling-data connectivity study was brainmap.org. This database was chosen as the only source because it provides specific and systematized fields of information and software-specific coding of activation coordinates that make possible precise, automatic and consistent selection of the sample to study. The Database of Brainmap (<http://brainmap.org>) was accessed utilizing Sleuth 2.3, open software provided by the same web site, on May 8, 2015. The search conditions were: (1) studies reporting BA22 activation; (2) studies using fMRI; (3) normal subjects; (4) activations: "activation only" (discarding report of de-activations); (5) right-handed subjects; (6) age 20–60 years; (7) native language: English; (8) domain: language. Visual inspection

of the results was utilized to filter only studies with paradigms assessing lexico-semantic functions. Twenty-two papers matched inclusion search criteria.

Exclusion criteria were used as well. Studies were excluded if they had bilingual subjects, tasks limited to expressive language, paradigms in patients, and paradigms in which language mediated the study of different domains (e.g., inhibition, attention load) or beyond the lexico-semantic sphere (e.g., expressive language, broad language target, etc.)

Based on these criteria 6 articles were excluded leaving 16 papers for further analysis. The pooling data consisted of 283 subjects, 21 experiments; and 241 foci or localizations (Table 1). Activation foci associated to BA22 (search criteria) were obtained automatically from the Sleuth software. This automatic report lists a number of clusters defined by the center of mass (in MNI coordinates), volume in  $\text{mm}^3$ , maxima intensity (peak), and neighboring BA's-peaks within 5 mm of the maxima plus and minus with respect the orthogonal coordinates (we will call them included), since these peaks are within the main cluster). Clusters are labeled accordingly with the maxima. These coordinates, per subject/task/paper were exported as text files (pooled results) for analysis on the following step.

Statistical significance of clusters found on the pooled-data was then analyzed utilizing the Activation Likelihood Estimate-(ALE) method [12]. This step was performed with the open source software GingerALE (<http://brainmap.org>). ALE treats reported peaks of activation as spatial probability distributions centered at the given coordinates. ALE computes the union of activation probabilities for each voxel, allowing differentiation between true convergence of activation foci from random clustering (noise). ALE scores obtained from thousands of random iterations are used to assign p-values to the observed clusters of activation. For more information on the theory of ALE the reader is advised to read the work of Eickhoff et al, 2009. Our ALE maps were threshold at  $p < 0.01$  corrected for multiple comparisons utilizing the *false discovery rate* method. Only clusters of 200 or more cubic mm were accepted as valid clusters. ALE results were overlaid onto an anatomical template suitable for MNI coordinates, also provided by BrainMap.org. For this purpose we utilized the Multi-Image Analysis GUI (Mango) (<http://ric.uthscsa.edu/mango/>). A mosaic of  $5 \times 6$  transversal-cut insets of fusioned images were obtained utilizing the same tool, selecting every 3–4 images starting on axial image No. 14, and exported the mosaic to a 2D-jpg image.

### 3. Results

13 significant clusters of activation were found with the ALE procedure. Table 1 shows these clusters ranked by their volume in cubic millimeters.

The main cluster corresponds to the left inferior frontal gyrus (BA44, BA45) and adjacent (included peaks) anterior insula (BA13), BA46 and BA47. The second cluster corresponds to left middle temporal gyrus, BA22, our search criteria-area. This cluster is just 10% smaller than the first one and depicts the local intra-area connectivity. As included peaks are BA41 (primary auditory),

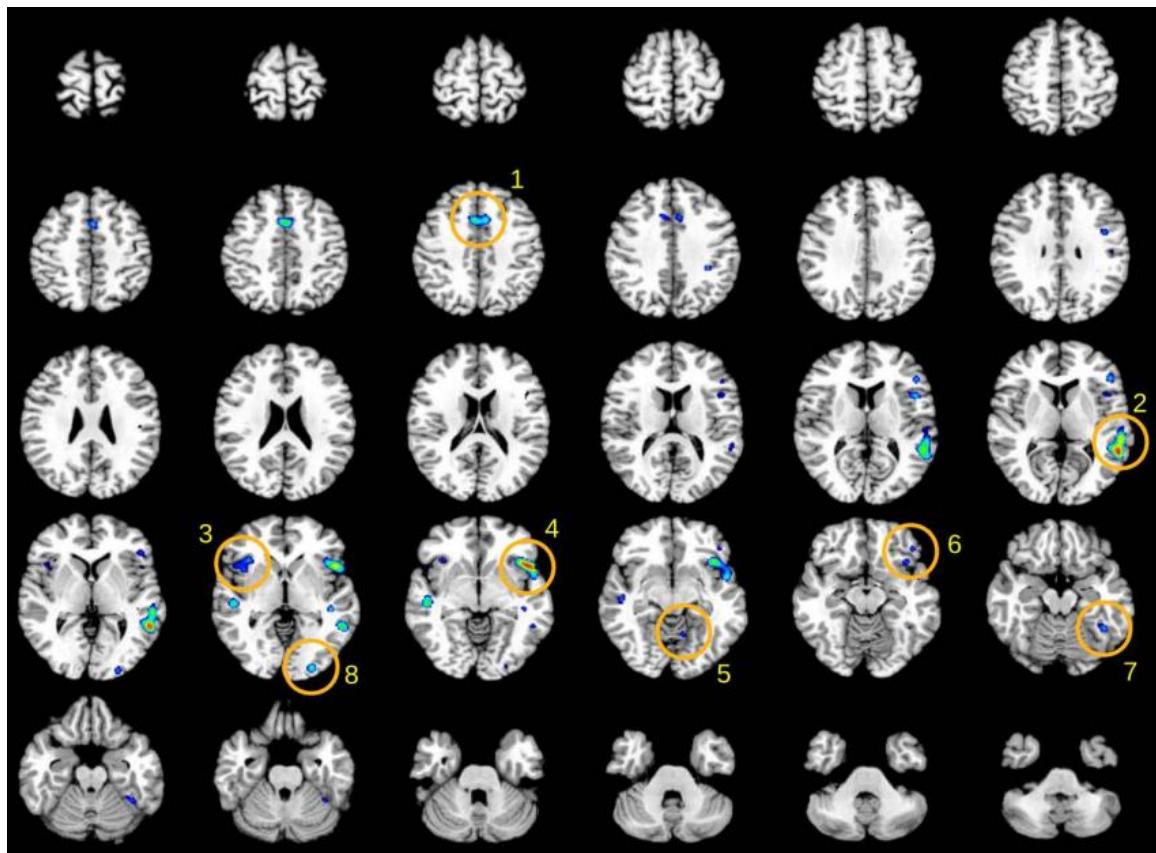
BA21 and BA37. The third cluster is located in the left medial frontal gyrus, more precisely in the pre-SMA corresponding with BA32. Included peaks in the cluster are left BA6 and right BA32.

**Table 1. BA22's network cluster list.**

Vol (mm <sup>3</sup> )	Center of mass			Peak maxima	Included Peaks
	x	y	z		(Vol > 200 mm <sup>3</sup> )
6632	-47.56	19.45	-1.98	Left BA44,45	Left BA13, BA46-47
6096	-57.25	-40.53	5.17	Left BA22	Left BA 41, BA21, BA37
2904	-1.01	15.23	43.33	Left BA32 (pre-SMA)	Left BA6, right BA32
1736	39.32	20.66	-1.97	Right BA13 (insula)	
1416	49.18	-20.37	-5.03	Right BA22	
1000	-40.6	-47.12	-20.35	Left BA37 (fusiform gyrus)	Left BA20
784	-26.4	-92.26	-1.19	Left BA18	
464	-44.97	-27.5	-2.78	Left BA22 (anterior)	
360	-43.6	3.21	30.37	Left BA6 (pre-motor area)	
336	-45.43	37.17	-12.16	Left BA47	
320	-11.58	-55.5	-11.38	Left cerebellar culmen	
256	34.62	-35.99	38	-Left BA40	
216	-49.28	-18.37	28.16	Left BA1,2,3 (post central gyrus)	

ALE report. Main loci of brain connectivity of Left Brodmann Area 22 (Wernicke's Area). Conventions: x, y, z: MNI coordinates; Vol, volume of cluster in cubic millimeters as a measure of activation extent.

The fourth and fifth clusters involved the right anterior insula (BA13) and the right middle/superior temporal gyrus (BA22) as mirror activations from the left but in much less extension. Indeed, the volume of the right BA22 activation is just 23.22% of the homologous left. Right BA13 cannot be compared as its contralateral activation is included within the entire cluster 1. The sixth cluster is represented by the left fusiform gyrus (BA37) with an included peak from BA20, while the seventh is located in the left visual area BA18. The eighth cluster is reported by the software as "left sub-lobar insula, BA22." Given the inconsistency of this report the images and raw foci pooled images were visually inspected. The inconsistent report seems to correspond actually to the deep anterior part of BA22, adjacent to the caudal aspect of the insula. The cluster localization has been changed accordingly. Cluster number 9 corresponds to left lateral frontal lobe (pre-motor) or BA6 activation. Clusters 10 to 13 with volumes inferior to 350 cubic mm, were found localized in the left BA47, left cerebellar culmen, left BA40 or inferior parietal lobule, and left primary somatosensory area (BA1, BA2, BA3). Figure 1 presents the main foci of brain connectivity of BA22.



**Figure 1. Functional connectivity map of BA22 by Meta-analytic Connectivity Modeling.** Insets in mosaic picture correspond to transversal descending cuts of the brain MRI template. Left hemisphere appears on the right side (Radiological convention). Clusters of activation are color coded for statistical significance from dark blue (lowest) to red (highest). Main cluster of the automatic ALE report are shown in numbered circles: BA6, 32 (1); left BA22 (2); right anterior insula (3); left BA44,45 and anterior insula (4); left cerebellar culmen (5); left BA47 (6); left BA37 (7); left BA18 (8).

#### 4. Discussion

We found that lexico-semantic network of BA22 consists of 13 clusters. Quite strikingly we found that the main cluster of activation includes the left infero-lateral frontal gyrus (BA44,BA45) and the anterior insula (BA13); BA44 and BA45 is the anterior language production system (Broca's area) whilst BA46 and BA47—left dorsolateral prefrontal cortex—are likely involved in executive control of language. The insula (BA13) has been suggested to have a crucial language role by integrating the receptive and expressive functions [13].

Activation of BA22 (cluster 2) is expected as it constitutes the source area for this search and reveal the spatial intrinsic local connectivity. Included peaks (BA41, BA21 and BA37), aggregated by their close proximity, are most likely associated to input (BA41) and output of BA22, BA37 via

short U fibers.

The supplementary (SMA)/pre-supplementary motor area, BA32, found included in this network (cluster 3) was unexpected as no structural connection to BA22 is known. SMA is connected structurally to BA44 through the aslant frontal fasciculus described by Catani and coworkers [14], and most likely associated with verbal fluency and initiation of speech [15]. BA32 is activated in a diversity of language-related tasks, such as verbal initiation [16], naming [17,18], and verbal fluency [19]. As such, BA32 may have a rather ancillary function in lexico-semantic analysis.

The activation of the right insula (cluster 4) is interesting. Processing of semantic violations activate the insular cortex bilaterally [20]. Further, right anterior insula activation has been described in tasks demanding semantic analysis across different language in bilingual subjects [21]. Recent studies with transcranial magnetic stimulation have found right lateralization in temporal areas for emotional prosody processing [22]. Thus, it seems that the right insula truly partakes in the semantic network.

The connectivity to left BA37 (posterior inferior temporal gyrus, middle temporal gyrus and fusiform gyrus), corresponding to cluster 5, reveals the importance of "access to word repository" in the process of lexico-semantic analysis or the access to visuo-spatial representation of objects and ideas in this area. Finding and producing words (word retrieval and word generation) are potential functions of BA37 considering that the destruction of this area is associated with word selection anomia [23,24]; some studies indeed have found that word search results in an increased activity in this area [25,26]. Moreover, the involvement of BA37 in naming has been well documented [e.g., 27–29]. Using a similar procedure to the one reported here, it was found that left BA37 is a common node of two distinct networks—visual recognition (perception) and semantic language functions [27].

The connectivity to right BA22 (cluster 5), shows that BA22 asymmetry for language is not complete. Indeed, the ratio of activation rBA22/lBA22 is 0.23. However, it is difficult to understand the right BA22. On one hand, lesional cases seem to show a potential language function for right BA22 as posterior aphasias recover better than anterior aphasias; but on the other hand, lesions of right temporal lobe, which includes BA22, usually do not affect language [23]. Cluster 8 shows a second peak on left BA22 which extends rostrally into the anterior half of the superior temporal gyrus, between BA38 and BA41. This area (antero-superior BA22) and BA47 process the meaning of sentences contingent to grammar construction, as explained below. It has also been described as critical for language comprehension by Turken and Dronkers [31].

The connectivity to left BA6 is most likely related to speech planning functions [32,33] as BA6 is a pre-motor area. Left BA6 has been reported activating in language processing tasks [34,35], language switching [36], object naming [37,38], lexical decisions [39] and syntactic processing [40]. It is difficult to rule out the mere effect of a speech/expressive language confound in the reported tasks, such as sub-vocalization, but functional connectivity of BA22 obtained with task-less resting-state fMRI also confirm strong BA22 to BA6 connectivity (author's observation: preliminary results in one normal subject are available at [http://www.fmriconsulting.com/brodmannconn/index.php?q=BA\\_22](http://www.fmriconsulting.com/brodmannconn/index.php?q=BA_22)).

The connectivity to left 47 is also understood within the language network. BA47 has a function in processing the meaning of sentences contingent to grammar construction (e.g., "John gave the book to Mary" vs. "John gave Mary a book") [41]. A recent study from Ardila et al [23] has demonstrated the involvement of this area in a network of expressive/receptive language. The authors suggest that this involvement is most likely of executive type, that is, as having functions in inhibition, planning, and production of language. It seems there is an intriguing interplay between receptive language (comprehension) and motor planning via speech/language production.

The participation of the cerebellar culmen (cluster 11) in semantic processing is not clear. Although there are several publications linking the cerebellum with language functions, there is no publications linking directly the culmen to language. Of note is the interesting finding of ipsilateral, and not contralateral, activation with respect cortical motor areas activated (BA6, BA44–47), which suggests a non-motor cerebellar involvement in lexico-semantic tasks.

Area BA40 (cluster 12) corresponds anatomically with the supramarginal gyrus. Left BA40 activates in semantic processing, mostly when complex semantic representations are required [4]. For example, left BA40 activates in sentences with transitive verbs, requiring agent and theme, (e.g., "The dog chased the boy") as compared to sentences with intransitive verbs, requiring only an agent as in "The dog sleeps" [42]. Left BA40 has also been found activating in task of verbal creativity [43]. Lesional transitory models like Transcranial Magnetic Stimulation validate also the role of BA40 in semantic processing. Left supramarginal gyrus stimulation (BA40) with this technique produces semantic errors [44].

The connections to BA18 (cluster 7) and BA1-3 (cluster 13) are intriguing as they are not putative language areas. Visual areas may be involved in verbal tasks as the subject "re-visualize" objects and scenes described by the verbal material; post-central gyrus may be involved as a consequence of accessing somatosensory "memories" in the meaning decoding process, in the same way that cortical motor activation has been described in semantic processing of tools [45], and activation of taste-related words includes the anterior insula, frontal operculum, lateral orbitofrontal gyrus, and thalamus all related with task perception [46]. Likewise the motor and premotor foci of activations referred here may be explained, at least in part, by accessing repositories of motor representations related to verbs [47,48].

Our results agree in part with the results published in the scant prior studies that utilizing different methods targeted directly or indirectly BA22 for connectivity. The comprehension network, that involves lexico-semantic analysis, and its connections have been previously demonstrated combining resting-state fMRI and Diffusion Tensor Imaging (DTI). The modules involved were BA22, BA46, BA47 and BA39 [31]. To our best of our knowledge our work is the first publication demonstrating the network of BA22 in lexico-semantic processing, utilizing pooling-data of co-activation, finding an extended network that involves left BA40, BA44, BA32, BA6 and bilateral insula.

The characterization of BA22-related language network as subserving a specific function is important to further develop and supports the view sustaining that cognitive functions are attributed

to network configurations and not to isolated modules. The description of these networks may help to dissect the contribution of basic into more complex functions. To attach a visual referent to a word (semantics) may require a port-of input, a lexical analyzer, a word-image repository or comparator. In addition, other modules may specifically intervene associated to the stimulus category. In that way the core semantic network may require to access motor schemes, sensory memories, emotion memories and valences, motor/cognitive inhibition and working memory fields.

The present study has some limitations. Our results are based in only one source data (brainmap.org). Many more articles have described BA22 activation in language tasks, but they have not been included in the Brainmap.org database. For a study to be included in Brainmap.org database, requires brain activation results to be reported in standard space coordinates (MNI or Talairach). Despite this limitation the authors estimate the number of studies/participants/experiments entering the pooling-data is large enough to provide statistical power and reflects the state of the art publications in fMRI of language.

## 5. Conclusions

We found that BA22 is basically connected with the anterior language production system (Broca's area BA44 and BA45; plus BA46 and BA47—left dorsolateral prefrontal cortex—likely involved in the executive control of language), the insula (BA13) (integrative node for the receptive/temporal and production/frontal language systems), BA37 (posterior inferior temporal gyrus, middle temporal gyrus and fusiform gyrus) which represents a common node of two distinct networks—visual recognition (perception) and semantic language functions; plus some other minor connections, including visual association areas in the occipital lobe (BA18) and the pre-supplementary motor area (BA32).

## Disclosures

Dr. Byron Bernal is owner and President of *fMRI Consulting Inc.*

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