

## Should Broca's area include Brodmann area 47?

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### Abstract

**Background:** Understanding brain organization of speech production has been a principal goal of neuroscience. Historically, brain speech production has been associated with so-called Broca's area (Brodmann area –BA- 44 and 45), however, modern neuroimaging developments suggest speech production is associated with networks rather than with areas. The purpose of this paper was to analyze the connectivity of BA47 (*pars orbitalis*) in relation to language. **Method:** A meta-analysis was conducted to assess the language network in which BA47 is involved. The Brainmap database was used. Twenty papers corresponding to 29 experimental conditions with a total of 373 subjects were included. **Results:** Our results suggest that BA47 participates in a "frontal language production system" (or extended Broca's system). The BA47 connectivity found is also concordant with a minor role in language semantics. **Conclusions:** BA47 plays a central role in the language production system.

**Key words:** Brodmann areas, BA47, Broca's area, language, meta-analysis, BrainMap, fMRI, Pars orbitalis.

### Resumen

*¿Debería el área de Broca incluir el área 47 de Brodmann?*

**Antecedentes:** la comprensión de la organización cerebral del lenguaje expresivo representa un reto importante para las neurociencias. Históricamente, la producción del lenguaje se ha asociado con la llamada área de Broca (área de Brodmann AB- 44 y 45); sin embargo, las técnicas contemporáneas de neuroimagen sugieren que la producción del habla se asocia con redes más que con áreas específicas. **Objetivos:** el propósito de este estudio fue analizar la conectividad del AB47 (*pars orbitalis*) con relación al lenguaje. **Método:** se llevó a cabo un meta-análisis para evaluar la red del lenguaje en la cual participa el AB47. Se utilizó la base de datos Brainmap. Se incluyeron 20 artículos correspondientes a 29 condiciones experimentales con un total de 373 sujetos. **Resultados:** nuestros resultados sugieren que el AB47 participa en un "sistema frontal de producción del lenguaje" (o sistema de Broca extendido). La conectividad de AB 47 hallada también es congruente con un papel menor en la semántica del lenguaje. **Conclusiones:** se concluyó que el AB47 juega un papel central en el sistema de producción del lenguaje.

**Palabras clave:** áreas de Brodmann, AB47, área de Broca, lenguaje, meta-análisis, BrainMap, fMRI, Pars orbitalis.

Traditionally, it has been accepted that speech production is controlled by the so-called Broca's area corresponding to Brodmann's area (BA) 44 (*pars opercularis* of the left inferior frontal gyrus) (e.g., Goldstein, 1948; Damasio & Geschwind, 1984; Head, 1926; Hécaen, 1972; Luria, 1947/1970). Since about some 20 years ago, it has been accepted that BA45 (*pars triangularis*) should also be included in Broca's area (e.g., Foundas et al., 1996). Some authors have proposed that BA47 (*pars orbitalis*) can also be included in a so-called "Broca's complex" (Hagort, 2005). Lemaire et al. (2013) refer to an "extended Broca's area" also including BA47, and Ardila et al. (2016) also proposed a "Broca's complex" including BA44, BA45, BA46, BA47, the mesial segment of BA6 (i.e., the supplementary motor area) and extending subcortically toward the basal ganglia. So, different authors have suggested that language production is controlled by a broader brain system not limited to the classical Broca's area; left BA47 (*pars orbitalis*) has

been proposed to be included in this broader language production system.

Recent functional studies have demonstrated that BA47 participates in different language functions, including, semantic processing (Left) (Chou et al., 2006; De Carli et al., 2006; Wong et al., 2002), semantic encoding (Demb & Glover, 1995; Li et al., 2000), semantic retrieval (Desmond et al., 1995; Lehtonen et al., 2005; Zhang et al., 2004), phonological processing (De Carli et al., 2007; McDermott et al., 2003), lexical inflection (Sahin, Pinker, & Halgren, 2006), syntactic processing (Tyler et al., 2011), and selective attention to speech (Vorobyev et al., 2004). Right BA47 has been related with affective prosody (Belyk & Brown, 2014; Wildgruber et al., 2005). However, left BA47 has been observed to participate not only in language but also in other domains such as working memory (e.g., Ranganath, Johnson, & D'Esposito, 2003) and deductive reasoning (Goel, Gold, Kapur, & Houle, 1998) (for a review of the function of BA47 found in functional studies see: <http://www.fmriconsulting.com/brodmann/>)

The significant amount of language-related functions that have been associated with BA47, such as semantic processing, phonological processing, semantic encoding, and others, is surprising. In these cases, it can be assumed that BA47 is simply one of the multiple steps in the brain language production network

(“Broca’s complex”). However, the specific participation of BA47 in a language production circuit undoubtedly requires further analysis. That is the goal of the current meta-analytic study. This study is the continuation of a research program devoted to analyzing the participation of different Brodmann areas in language (Ardila, Bernal, & Rosselli, 2014a, 2014b; 2015; 2016a, 2016b, 2016c; Bernal, Ardila, & Rosselli, 2015, Rosselli, Bernal, & Ardila, 2015).

Nowadays there are several techniques that can potentially demonstrate brain circuitries or networks (Friston, 2011; Li, Guo, Nie, & Liu, 2009). These techniques are grouped under the term “brain connectivity”. Recently, a new alternative to studying brain connectivity has been proposed by Robinson et al. (2010) known as *meta-analytic connectivity modeling* or MACM. MACM is based in automatic meta-analysis done by pooling co-activation patterns. The technique takes advantage of Brainmap.org’s repository of functional MRI studies, and of special software (Sleuth) provided by the same group, to find, filter, organize, plot, and export the peak coordinates for further statistical analysis of its results. Sleuth provides a list of foci, in Talairach or MNI coordinates, each one representing the center of mass of a cluster of activation. The method takes the region of interest (for instance, BA46), makes it the independent variable, and interrogates the database for studies showing activation of the chosen target. The query is easily filtered with different conditions (such as age, normal vs. patients, type of paradigm, domain of cognition, etc.). By pooling the data with these conditions the tool provides a universe of co-activations that can be statistically analyzed for significant commonality. As a final step, Activation Likelihood Estimation (ALE) (Laird et al., 2005; Turkeltaub et al., 2002) that can be performed utilizing GingerALE, another piece of software also provided by Brainmap, assesses the probability of an event occurring at voxel level across the studies. Areas of coactivation will show a network related to the function and domains selected as filter criteria. A diversity of studies have used this procedure to investigate brain connectivity (e.g., Kohn et al., 2014; Laird et al., 2009; Torta & Cauda, 2011; Zald et al., 2014).

Considering the complex role of BA47 in language, a meta-analytic connectivity analysis utilizing MACM on the participation of BA47 in language was developed. The objective of this study as to analyze the left BA47 participation in the brain language networks associated with different language functions. The present study is aimed to support the involvement of BA47 in a brain language production system.

## Method

### Participants

Twenty papers corresponding to 29 experimental conditions with a total of 373 subjects were selected (subjects participating in two different experiments were counted as two subjects) (Table 1).

### Instruments

A meta-analysis of fMRI studies was developed.

### Procedure

The Brainmap database (brainmap.org) was accessed utilizing Sleuth 2.2 on August 2, 2015. Sleuth is the software provided by

Brainmap to query its database. The meta-analysis was intended to assess the network of coactivations in which BA47 is involved.

The search conditions were: (1) studies reporting BA47 activation; (2) studies using fMRI ; (3) context: normal subjects; (4) activations: activation only; (5) handedness: right-handed subjects; (6) age 18-60 years; (7) domain: cognition, subtype: language; (8) Language: English.

### Data analysis

(ALE) meta-analysis was then performed utilizing GingerALE. ALE maps were thresholded at  $p < 0.01$  corrected for multiple comparisons and false discovery rate. Only clusters of 200 or more cubic mm where 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/>). Mosaics of  $7 \times 7$  insets of transversal fusion images were generated utilizing a plugin of the same tool, selecting every other image, and exported to a 2D-jpg image.

## Results

Table 2 presents the main loci of brain connectivity of BA47 by Meta-analytic Connectivity Modeling (MACM). Nine different clusters of activation were found, mostly related to the left hemisphere (Figure 1).

*Table 1*  
Studies of language paradigms included in the meta-analysis

| Publication           | Paradigm                          | n  | Foci |
|-----------------------|-----------------------------------|----|------|
| Booth et al., 2002    | Visual Rhyming - Control          | 13 | 11   |
|                       | Auditory Meaning - Control        | 13 | 9    |
|                       | Meaning - Rhyming                 | 13 | 8    |
| Mechelli et al., 2000 | Pseudowords - Rest                | 6  | 2    |
|                       | Pseudowords - Words               | 6  | 7    |
| Dapretto et al., 1999 | Syntactic vs. Rest                | 8  | 8    |
|                       | Semantic vs. Rest                 | 8  | 8    |
|                       | Semantic vs. Syntactic            | 8  | 1    |
| Devlin et al., 2003   | Semantic + Phonological - Rest    | 12 | 26   |
|                       | Phonological > Semantic           | 12 | 34   |
| Noppeney et al., 2004 | Abstract> Sounds, Visual, Hand    | 15 | 4    |
| Jackson et al., 2004  | Associative Encoding - Fixation   | 12 | 61   |
|                       | Successful Associ -Unsucces Assoc | 12 | 10   |
| Binder et al., 2003   | Word > Nonword                    | 24 | 26   |
| Tagamets et al., 2000 | Words vs. Shapes                  | 11 | 18   |
|                       | Pseudowords vs. Shapes            | 11 | 20   |
| Booth et al., 2002    | Rhyming, Vis - Aud                | 13 | 5    |
| Peck et al., 2004     | Sent Gen vs. View Nonsense Obj    | 10 | 13   |
| Rowan et al., 2004    | Verb Generation – Activations     | 10 | 13   |
| Leff et al., 2008     | Idioms + Rearranged Idioms        | 23 | 3    |
| Damasio et al., 2001  | Action Tool Word Retrieval        | 20 | 7    |
| Sharp et al., 2010    | Semantic Perceptual               | 12 | 5    |
| Davis et al., 2008    | Words vs. Letter Strings          | 12 | 9    |
| Desai et al., 2006    | Generate Regular Verbs - Read     | 25 | 21   |
| Longe et al., 2007    | Inflections vs. Baseline          | 12 | 14   |
| Tyler et al., 2004    | Words - Letter Strings            | 12 | 14   |
| Diaz et al., 2011     | Metaphor > Literal                | 16 | 6    |
| Lee et al., 2006      | Literal > Rest                    | 12 | 21   |
|                       | Nonliteral > Rest                 | 12 | 20   |

*Table 2*  
Main loci of brain connectivity of BA47 in language tasks by Meta-analytic Connectivity Modeling (MACM)

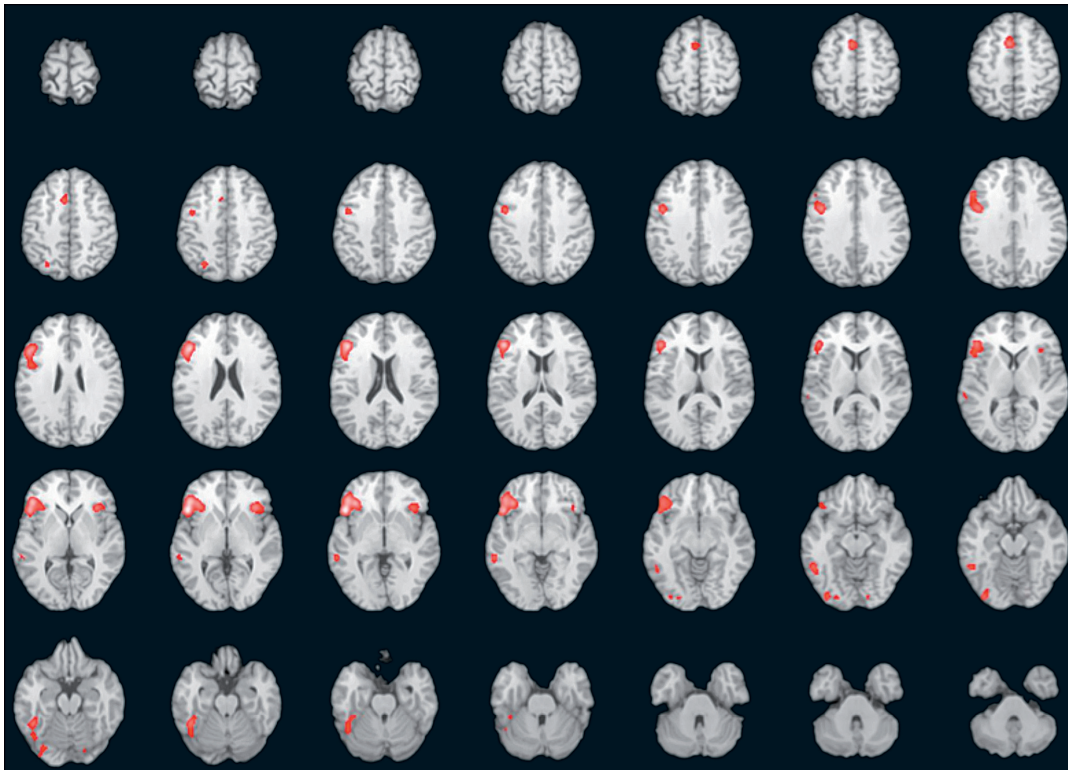
| Region (BA)                      | x   | y   | z   | ALE   | Volume (mm <sup>3</sup> ) |
|----------------------------------|-----|-----|-----|-------|---------------------------|
| <b>Cluster #1</b>                |     |     |     |       |                           |
| L. Inferior frontal gyrus (47)   | -46 | 18  | -2  | 0.051 | 16120                     |
| L. Middle Frontal gyrus (46)     | -44 | 24  | 20  | 0.044 |                           |
| L. Inferior frontal gyrus (47)   | -44 | 28  | 0   | 0.433 |                           |
| L. Inferior gyrus (47)           | -34 | 26  | -4  | 0.383 |                           |
| L. Precentral gyrus (6)          | -42 | 0   | 28  | 0.315 |                           |
| <b>Cluster #2</b>                |     |     |     |       | 3328                      |
| L. Cerebellum culmen             | -44 | -50 | -20 | 0.029 |                           |
| L. Inferior temporal lobe (20)   | -52 | -52 | -12 | 0.260 |                           |
| L. Cerebellum declive            | -42 | -66 | -18 | 0.021 |                           |
| <b>Cluster #3</b>                |     |     |     |       |                           |
| R. Insula (13)                   | 36  | 22  | 0   | 0.032 | 1992                      |
| <b>Cluster #4</b>                |     |     |     |       |                           |
| L. Frontal lobe superior (6)     | -4  | 8   | 48  | 0.031 | 1800                      |
| <b>Cluster #5</b>                |     |     |     |       |                           |
| L. Inferior occipital gyrus (18) | -34 | -88 | -14 | 0.026 | 1144                      |
| L. cerebellum declive            | -32 | 80  | -16 | 0.021 |                           |
| <b>Cluster #6</b>                |     |     |     |       |                           |
| L. Middle temporal gyrus (21)    | -58 | -40 | -4  | 0.026 | 1104                      |
| L. Middle temporal gyrus (22)    | -58 | -36 | 6   | 0.018 |                           |
| <b>Cluster #7</b>                |     |     |     |       |                           |
| L. Superior parietal (7)         | -26 | -66 | 42  | 0.023 | 464                       |
| <b>Cluster #8</b>                |     |     |     |       |                           |
| L. Inferior occipital (18)       | -22 | -88 | -10 | 0.018 | 248                       |
| <b>Cluster #9</b>                |     |     |     |       |                           |
| R. Lingual gyrus (18)            | 16  | -88 | -12 | 0.017 | 224                       |
| R. Cerebellum declive            | 20  | 82  | -18 | 0.016 |                           |

The first cluster includes the frontal areas 46, 47, and 6 in the left hemisphere. Noteworthy, this as an extensive cluster with a volume about five times larger than Cluster #2 and about eight times larger than Cluster #3. Indeed, the rest of the activation clusters are relatively small.

The second cluster includes the left insula and the anterior cerebellum, but most likely the source of activation is located in the fusiform gyrus (BA37); the simultaneous activation in the same cluster of the Inferior temporal lobe (BA20) emphasizes the activation of BA37. Cluster #3 refer to the right insula. Cluster #4 is located in the left superior frontal lobe superior (BA6) consequently corresponding to the supplementary motor area. Cluster #5 is located in the left inferior occipital gyrus (BA18). Cluster #6 is the Wernicke's area (BA21 and BA22). The last three clusters are small and are located in the left superior parietal area (BA7), left inferior occipital lobe (BA18), and anterior right cerebellum (quite likely, the fusiform gyrus).

## Discussion

It is well known that BA47 has some participation in language, although pinpointing its specific function has not been easy. It has been suggested that the major language functions include semantic and phonological processing, grammatical processing (including lexical inflection and syntactic processing, and selective attention to speech (see Brodmann's Interactive Atlas). Because of its location in the brain (below Broca's area), it is understandable that BA47 participates in language production and grammar. However, it has also been proposed that BA47 may participate in some other functions. Levitin & Menon (2003) have suggested that BA47 may be more generally responsible for processing fine-structured stimuli that evolve over time, not merely those that are linguistic.



**Figure 1.** Language-related BA47's network. ALE results overlaid on an axial-T1 MRI MNI-template. Left hemisphere appears in the left side of the insets (neurological convention). ALE scores are color coded from red (lower scores) to white (higher scores). In addition to the left BA47 (Inferior frontal gyrus - Pars orbitalis) that has the highest intensity, the following regions appear "activated": BA46, BA6, BA13, BA37, BA20, BA21, BA22, BA7 and BA18

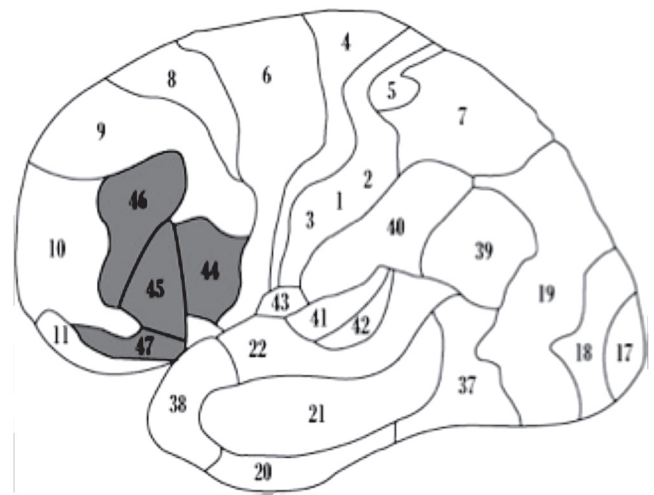
Functional and clinical studies corroborate the involvement of BA47 in language production. Neuroimaging studies have demonstrated that brain areas activated during speaking are notoriously larger than the classical Broca's area (Ardila, Bernal, & Rosselli, 2016d; Gernsbacher & Kaschak, 2003; Pickering & Garrod, 2013). This extended brain activation during language production has been demonstrated using diverse techniques such as magnetoencephalography (MEG) (Salmelin, 2007). From the clinical point of view, it is well known that damage restricted to Broca's area does not result in the classical Broca's aphasia; extension to the insula, lower motor cortex (including BA47), and subjacent subcortical and periventricular white matter is required (Alexander, Naeser, & Palumbo, 1990; Benson & Ardila, 1996).

In the current meta-analytic study it was found a major cluster of coactivation, including BA46, BA47, and BA6 in the left hemisphere. That means, during linguistic tasks BA47 become activated simultaneously with other frontal adjacent areas, conforming a single focus of activation. The second of activation cluster included the left insula and some posterior language areas (BA37 and BA20), suggesting (as it has been reported in the literature) and involvement of BA47 is semantic aspects of the language. The rest of the clusters were indeed small, and locate in parietal and occipital areas.

Current results illustrate that BA47, (1) participates in a frontal language production system, which probable includes not only the classical Broca's area, but also BA46 and the medial extension of BA6, corresponding to the supplementary motor area, and some subcortical areas ("Broca complex", Ardila, Bernal, & Rosselli, 2016c) (Figure 2); (2) it also has a secondary participation in semantic processing; coactivation with left temporal areas involved in semantic processing (BA37 and BA20).

Many limitations could be mentioned regarding the present study. The major critique of meta-analysis studies commonly refers to the lack of homogeneity of the pooled tasks, methods, and individuals. Furthermore, MACM is still new requiring performance of future validation studies. We have used BA47 as the independent variable and a spectrum of co-activated areas as the dependent variable, which may be unusual.

As mentioned before, there are diverse techniques that potentially could be used to detect brain connectivity. Each one of the available techniques to study brain connectivity have some advantages but also disadvantages. According to Friston (2011) the



**Figure 2.** "Broca's complex" includes BA44, BA45, BA46, BA47, mesial BA6 (supplementary motor area; not seen) and extending subcortically toward the basal ganglia and the thalamus (not seen) (according to Ardila et al., 2016b)

most prevalent approaches to effective connectivity analysis are dynamic causal modeling (DCM), structural equation modeling, and Granger causality; however, each of them have some important limitations. Li et al. (2009) propose to divide the computational methodologies used to analyze brain connectivity using fMRI into two general categories: model-driven methods and data-driven methods. Data driven methods are a large family, and thus are further sub-classified into decomposition-based methods and clustering analysis methods. In our study we used a cluster analysis approach. According to these authors, a major limitation of cluster analysis is that it is based on intensity proximity that may be not enough for functional connectivity detection in fMRI. This is obviously an additional limitation of our study. However, the current results are quite consistent with clinical observations, positively supporting the structural connectivity findings.

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