

Connectivity of BA46 involvement in the executive control of language

Alfredo Ardila¹, Byron Bernal² and Monica Rosselli³

¹ Florida International University, ² Miami Children's Hospital and ³ Florida Atlantic University

Abstract

Background: Understanding the functions of different brain areas has represented a major endeavor of contemporary neurosciences. Modern neuroimaging developments suggest cognitive functions are associated with networks rather than with specific areas. Objectives. The purpose of this paper was to analyze the connectivity of Brodmann area (BA) 46 (anterior middle frontal gyrus) in relation to language. **Methods:** A meta-analysis was conducted to assess the language network in which BA46 is involved. The DataBase of Brainmap was used; 19 papers corresponding to 60 experimental conditions with a total of 245 subjects were included. **Results:** Our results suggest the core network of BA46. The localization and modules involved suggest BA46 participation in a "frontal language production system" (or extended Broca's system). The depicted BA46 connectivity is also concordant with a minor role in language semantics and language understanding. **Conclusion:** It was concluded that BA46 plays a central role in the language production system, most likely related to its executive control.

Keywords: BA46, meta-analysis, fMRI, language.

Resumen

Estudio de la conectividad del BA46 en el control ejecutivo del lenguaje.

Antecedentes: la comprensión de las funciones de diferentes áreas cerebrales representa una de las mayores empresas de las neurociencias contemporáneas. Los estudios contemporáneos con neuroimágenes sugieren que las funciones cognitivas se asocian con redes más que con áreas específicas. El propósito de este estudio fue analizar la conectividad del área de Brodmann 46 (BA46) (circunvolución frontal media anterior) con relación al lenguaje. **Método:** se llevó a cabo un meta-análisis para determinar el circuito o red lingüística en la cual participa BA46. Se utilizó la base de datos Brainmap; se incluyeron 19 artículos correspondientes a 60 condiciones experimentales con un total de 245 sujetos. **Resultados:** nuestros resultados sugieren un papel central de BA46 en la red del lenguaje. BA46 participa en un "sistema frontal de producción del lenguaje" (o sistema de Broca extendido). La conectividad hallada es también congruente con una participación menor en la semántica y la comprensión del lenguaje. **Conclusiones:** se concluye que BA46 juega un papel central en el sistema de producción del lenguaje, muy probablemente relacionado con su control ejecutivo.

Palabras clave: BA46, meta-análisis, fMRI, lenguaje.

Although executive functions depend on extended dynamic networks including different brain areas (Koziol & Budding, 2009; Stuss & Alexander, 2007; Tonkonogy & Puente, 2009), it is well known that the prefrontal cortex plays a major controlling and monitoring role (Jurado & Rosselli, 2007; Stuss & Knight, 2002). The prefrontal areas of the frontal lobes (granular frontal cortex) can be regarded as association areas or intrinsic cortical areas (Mesulam, 2002). Luria (1980) considers that the prefrontal regions correspond to tertiary areas (which participate in processing information of various types) of the cerebral cortex. As a matter of fact, the prefrontal lobes maintain extensive connections, particularly with other cortical areas, the limbic system, the cortical and subcortical motor areas, and the sensory cortex (Damasio & Anderson, 2003).

Frequently, three different prefrontal syndromes associated with specific disturbances in executive functions are separated (e.g., Chayer & Freedman, 2001): Dorsolateral, medial and orbitofrontal. It has been proposed that these three prefrontal subsystems can be reduced to only two: dorsolateral and medial/orbital (Ardila, 2008). The first one (dorsolateral) relates to cognition control (metacognition). Dysfunction in this region disrupts essential component cognitive processes, including impairments in working memory, abstracting difficulties, and inability to organize a behavioral response to novel or complex stimuli (Fuster, 2008; Stuss & Alexander, 2000). Various researchers, including Luria (1980), have noted perseveration, stimulus bound behavior, echopraxia, and echolalia. According to Fuster (2001, 2002, 2008), the most general executive function of the lateral prefrontal cortex is temporal organization of goal-directed actions in the domains of behavior, cognition, and language.

Lateral differences are observed: whereas left prefrontal damage is more directly associated with cognitive processes, right damage is associated with both restriction of affect and emotional dyscontrol and defects in the perception or comprehension

of emotional information (Goldberg, 2001; Grafman, 2006). Anosognosia, impaired empathy, and defects in the appreciation of humor (Shammi & Stuss, 1999) are also found. Following lesion to the right dorsolateral area, a transcortical motor aprosodia is expected (Ross, 1981), whereas a left-sided dorsolateral lesion will produce a decline in verbal fluency on word generation tasks and so-called extrasylvian (transcortical) motor aphasia (Ardila, 2014; Berthier, 1999).

Extrasylvian (transcortical) motor aphasia due to lesions affecting the left dorsolateral prefrontal cortex is characterized by non-fluent language, good comprehension, and good repetition. Therefore, prosody, articulation, and grammar are preserved. The patient presents long latencies in language when beginning to speak or when answering questions. Open questions are slow and incomplete, and the patient tends to repeat the words included in the question. Expressive language is limited with some tendency to echolalia and perseveration; occasionally verbal paraphasias are observed. This type of aphasia has been interpreted as a language disturbance at the pragmatic level (use of the language according to the specific social context) (Benson & Ardila, 1996; Berthier, 1999).

The core Brodmann area (BA) in the dorsolateral prefrontal cortex is BA46. BA46 is known as anterior middle frontal gyrus. Actually, BA46 roughly corresponds with the dorsolateral prefrontal cortex. In the human brain it occupies approximately the middle third of the middle frontal gyrus and the most rostral portion of the inferior frontal gyrus (Mesulam, 1986, 2002). Interestingly, BA46 is regarded as one of the most recently evolved parts of the human brain that undergoes a prolonged period of maturation that lasts until adulthood (Collins, 2001).

Contemporary neuroimaging technique studies have supported the hypothesis regarding an active involvement of BA46 in linguistic processes (see Brodmann's Interactive Atlas), including verbal fluency (Abrahams et al., 2003), phonological processing (Heim, Opitz, Müller, & Friederici, 2003), semantic processing (Wang, 2008), and language comprehension (Turken & Dronkers, 2011). Taken together, all these findings support the conclusion that BA46 significantly participates in language. Furthermore, they suggest that it is not involved in a single linguistic process, but simultaneously in several verbal abilities.

It is noteworthy that the BA46 possesses extensive intracortical as well as fronto-subcortical connections (Cummings, 1983; Damasio & Anderson, 2003). Advancing the analysis of the functional connectivity of BA46 becomes most important in understanding its real contribution to the language brain system.

Currently, there are several techniques that can potentially demonstrate brain circuitries or networks. These techniques are grouped under the term "brain connectivity". Recently, a new alternative to study 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 the Brainmap.org's repository of functional MRI studies, and of a special software (Sleuth) provided by the same group, to find, filter, organize, plot, and export the peaks 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 software also provided by Brainmap, assesses the probability of an event to occur at voxel level across the studies. Areas of coactivation will show a network related to the function and domains selected as filter criteria.

Considering the complex role of BA46 in language, a meta-analytic connectivity analysis utilizing MACM on the participation of BA46 in language was developed. The objective of this study as to analyze the left BA46 participation in the brain language circuits associated with different language functions.

Methods

Procedure

The DataBase of Brainmap (brainmap.org) was accessed utilizing Sleuth 2.2 on January 2, 2014. Sleuth is the software provided by Brainmap to query its database. The meta-analysis was intended to assess the network of coactivations in which BA46 is involved.

The search conditions were: (1) studies reporting BA46 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 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/>). Mosaics of 5 x 6 insets of transversal fusion images were generated utilizing a plugin of the same tool, selecting every other image, starting on image No. 10, and exported to a 2D-jpg image. A 3D rendition of the brain was also obtained. The left hemisphere lateral view has been chosen for display.

Results

Nineteen papers corresponding to 60 experimental conditions with a total of 245 subjects were selected (subjects participating in two different experiments were counted as two subjects) (Table 1).

Table 2 presents the main loci of brain connectivity of BA46 by Meta-analytic Connectivity Modeling (MACM). Eleven different clusters of activation were found, mostly related to the left hemisphere (Figure 1 and Figure 2).

The first cluster includes the frontal areas 6, 44, 45, 46, and 47 in the left hemisphere. That is, the whole frontal system involved

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

Publication	Paradigm	n	Foci
Booth et al., 2002	Visual Rhyming – Control	13	11
	Visual Meaning – Rhyming	13	3
	Meaning – Rhyming	13	8
Dapretto & Bookheimer, 1999	Semantic vs. Rest	8	8
Devlin et al., 2003	Semantic + Phonological - Rest	12	26
	Phonological > Semantic	12	34
Kang et al., 1999	Syntactic VPs - Fixation	14	7
	Semantic VPs - Fixation	14	7
Schlosser et al., 1998	Verbal Fluency > Baseline	6	9
Jackson & Schacter, 2004	Associative Encoding - Fixation	12	61
Poldrack et al., 2001	Rhyme Judgment	8	2
	Convex Compression Response	8	5
Peck et al., 2004	Sentences vs. Viewing Objects	10	13
Rowan et al., 2004	Verb Generation	10	13
Damasio et al., 2001	Action Tool Word Retrieval	20	7
	Action Word Retrieval	20	9
	Concrete Entities - Picture Control	20	5
Simmons et al., 2008	Word Assoc > Situation Generation	10	32
	Early > Late Property Generation	10	26
	Early > Late, Word Assoc > Sit Gen	10	3
Sharp et al., 2010	Semantic Low Percept High Dif vs. Semantic Low Perceptual Low Dif	12	2
	Semantic High Perceptual Low Dif vs. Semantic Low Perceptual High Dif	12	5
Davis et al., 2008	All Words vs. Letter Strings	12	9
Desai et al., 2006	Generate Regular Verbs vs. Read Regular Present Tense Verbs	25	21
	Generate Irregular Verbs vs Read Irregular Present Tense Verbs	25	25
	Areas Correlated with Response Time	25	31
Longe et al., 2007	Inflections (Nouns + Verbs) vs. Baseline	12	14
Sabsevitz et al., 2005	Concrete > Abstract	28	26
Bedny et al., 2006	Words (Nouns + Verbs) > Non-words	13	6
Rosen et al., 2000	Word Stem Completion - Fixation	8	7
Tan et al., 2003	Rhyme Decision English	12	4

Table 2
Main loci of brain connectivity of BA46 in language tasks by Meta-analytic Connectivity Modeling (MACM)

Region (BA)	x	y	z	ALE	Volume (mm ³)
Cluster #1					
L Middle frontal gyrus (46)	-46	34	8	0.043545	18,904
L Precentral frontal gyrus (6)	-50	6	24	0.031531	
L Inferior frontal gyrus (47)	-36	28	-10	0.031294	
L Inferior frontal gyrus (45)	-48	22	-6	0.030777	
L Inferior frontal gyrus (44)	-54	14	40	0.030316	
Cluster #2					
R Insula (13)	48	16	-4	0.028763	2,424
R Insula (13)	40	24	-4	0.024963	
Cluster #3					
L Fusiform gyrus (37)	-42	-50	-20	0.024459	1,728
L Cerebellum culmen	-36	-46	-28	0.018386	
Cluster #4					
L Fusiform gyrus (37)	-52	-48	-2	0.022463	1,288
L Inferior temporal gyrus (20)	-54	-54	-12	0.019619	
Cluster #5					
L Occipital (18)	-24	-94	-4	0.019987	568
Cluster #6					
L Medial frontal lobe (32)	-8	18	44	0.020837	512
Cluster #7					
R Middle frontal gyrus (46)	50	30	18	0.022843	488
Cluster #8					
L Superior parietal (7)	-26	-66	50	0.020237	432
Cluster #9					
L Superior temporal lobe (22)	-46	-24	0	0.016397	296
L Middle temporal lobe (21)	-48	-30	-4	0.016394	
Cluster #10					
L Middle occipital (19)	-32	-76	26	0.017609	288
Cluster #11					
L Lenticular	-26	14	2	0.01659	256

in language production. Noteworthy, this as an extensive cluster with a volume about eight times larger than Cluster #2 and about 11 times larger than Cluster #3. Indeed, the rest of the activation clusters are relatively small.

The second cluster includes the right insula. Cluster #3 includes the left fusiforme gyrus (most likely activation of the culmen of

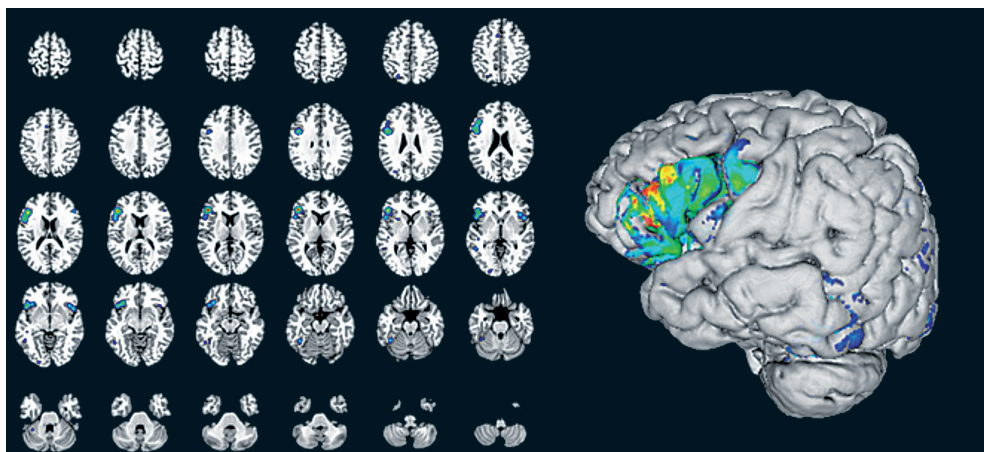


Figure 1. Functional connectivity map of BA46 by Meta-analytic connectivity modeling. Left side of the panel: transversal descending cuts of the brain MRI template. Left hemisphere appears on the left side (neurological convention). Clusters of activation are color coded for statistical significance from dark blue (lowest) to red (highest). Right side of the panel: 3D volumetric rendition of the brain showing activation on the left hemisphere surface. Red color zone identifies BA46. Deep and midline activations are not shown

the cerebellum is explained by the smoothing effect of the adjacent activation of the left fusiform gyrus). Cluster #4 includes the left fusiform gyrus as well as its anterior extension (BA20). Cluster #5 and Cluster #10 refer to the left occipital lobe; whereas Cluster #7 corresponds to the right BA46. Cluster #8 is located in the superior parietal lobe. Cluster #9 corresponds to the Wernicke's area. And finally, Cluster #11 refers to the left basal ganglia.

Discussion

The main connectivity revealed by the extent and intensity of the principal clusters with expressive areas makes evident that BA46 basically participates in a language production system, which also includes BA44, BA45, BA47, and BA6 in the left frontal lobe. This system could be referred as the "frontal language production system", or simply, the "Broca's system" and in the current study it presents very small co activation with other brain areas. Noteworthy, functional studies have demonstrated that BA6 is involved in diverse language functions, including speech motor programming (Fox et al., 2000; Shuster & Lemieux, 2005), phonological processing (McDermott et al., 2003), language switching (Price, Green, & Von Studnitz, 1999), and even syntactic processing (Inui et al., 1998). The medial extension of BA6 corresponds to the supplementary motor area, a brain area clearly involved in language processing (De Carli et al., 2007; Basho et al., 2007). The involvement of BA44, BA45, and BA47 in language production, on the other hand, is quite obvious (Hickok & Poeppel, 2004; Grodzinsky & Amunts, 2006; Price, 2010).

The connections with the insula (Cluster #2) are understandable. Functional studies have demonstrated that the insula represents a core area in language processing, extensively connected with anterior and posterior language areas (see Ardila, Bernal, & Rosselli, 2014). Insular damage has been associated with aphasia

since the 19th century (Wernicke, 1874). Thus, it is quite evident the role of the insula in diverse language functions (Ardila, 1999). However, it was quite surprising to find the activation in the right insula. It does not seem easy to find an explanation to the right-lateralized activation.

BA46 turned out to have some connections with posterior language areas involved in phonological, lexical, and semantic language processing (BA20, BA21, BA22 and BA37); these connections, however, are notoriously weaker than the connections with the rest of the frontal language production system (BA44, BA45, BA47, and BA6). The volume of Cluster #4 (BA37 and BA20) is some 14 times smaller than the volume of Cluster #1 ("language production system": BA44, BA45, BA47, and BA6). The volume of Cluster #9 (Wernicke's area: BA21 and BA22) is over 60 times smaller than the volume of Cluster #1. Evidently, the primary role of BA46 in language is related with language production control, not with phonological, lexical or semantic understanding. This is a conclusion easy to draw just taking a look of Figure 1 (right).

BA46 significant –albeit weak– connection with left BA37 (fusiform gyrus) is particularly interesting. It has been pointed out that left BA37 is a common node of two distinct networks - visual recognition (perception) and semantic language functions (Ardila, Bernal, & Rosselli, 2015). Many of the tasks included in the current analyses involved semantic decisions using visual information. Therefore, results suggest certain involvement of BA46 in visual/semantic associations of words and language understanding. Noteworthy, two clusters (Cluster #5 and Cluster #10) point to some connections of BA46 with the occipital lobe. The co-activation of the occipital lobe is not totally unexpected considering the existence of a fasciculus going between the occipital lobe and the prefrontal cortex: the inferior occipitofrontal fasciculus. It has been suggested that this fasciculus is involved

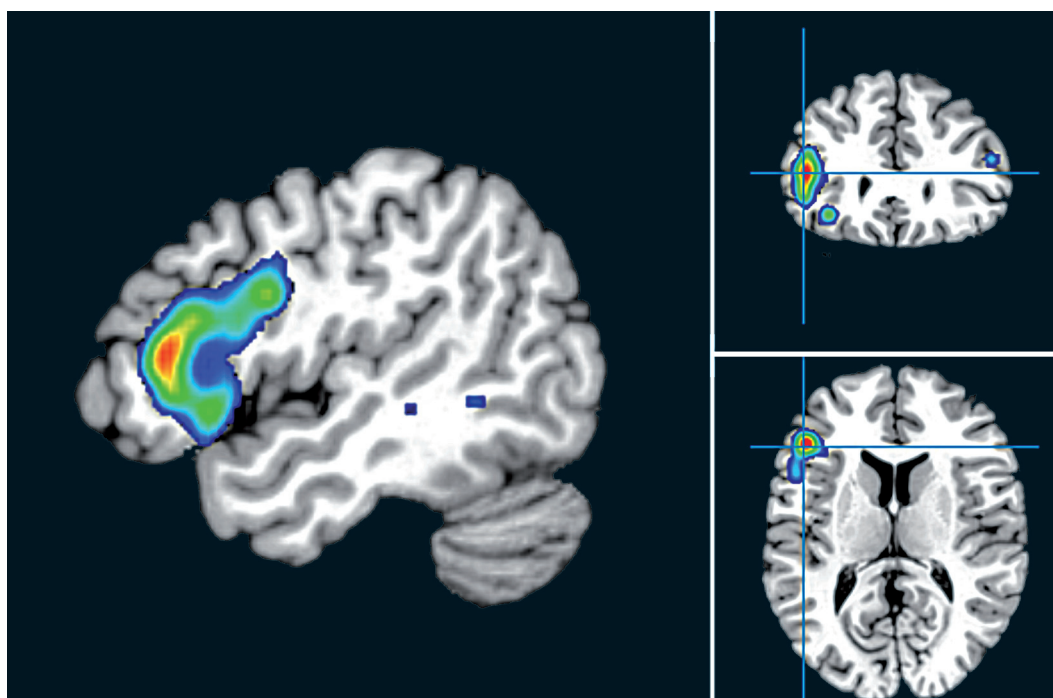


Figure 2. Functional connectivity map of BA46. Deep activations are shown

in language processing (Duffau et al., 2009; Mandonnet et al., 2007). Furthermore, it has been observed that this fasciculus has two branches: (1) a superficial and dorsal branch, which connects the frontal lobe with the superior parietal lobe and the posterior portion of the superior and middle occipital gyri; and (2) a deep and ventral branch, which connects the frontal lobe with the posterior portion of the inferior occipital gyrus and the posterior temporo-basal area. This observation is congruent with the role of this fasciculus in the semantic system, by showing that it is mainly connected with two areas involved in semantics: the occipital associative extrastriate cortex and the temporo-basal region (Martino et al., 2010).

The weakest cluster observed in this analysis was Cluster #11 (left lenticular nucleus). Indeed, the frontal cortex, including the dorsolateral prefrontal area, has extensive connections with subcortical areas, in particular with the striatum (Damasio & Anderson, 2003; Mesulam, 2002). Complex behavior has been

frequently related with fronto-subcortical circuits (Bonelli & Cummings, 2007; Cummings, 1993).

Regardless of the diverse limitations that can be pointed to the present study (specific characteristics of the sample, implicit limitations of the method that was used, inclusion of language as a whole without distinguishing different language abilities, etc.) it can be concluded that BA46 is involved together with BA44, BA45, BA47 and BA6 in kind of “frontal language production system” (or “Broca’s system”). A notoriously smaller albeit significant participation is also observed in language semantics and language understanding. Furthermore, considering that BA46 is the core dorsolateral prefrontal area involved in cognition control (metacognition), it can be suggested that BA46 plays the executive control in this frontal language production system; as a matter of fact, when BA46 is damaged, no active language production is observed (extrasyllabic or transcortical motor aphasia; Benson & Ardila, 1996; Berthier, 1999).

References

- References marked with an asterisk indicate studies included in the meta-analysis.
- Abrahams, S., Goldstein, L. H., Simmons, A., Brammer, M. J., Williams, S. C., Giampietro, V. P., Andrew, C. M., & Leigh, P. N. (2003). Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Human Brain Mapping, 20*(1), 29-40.
- Ardila, A. (1999). The role of insula in language: An unsettled question. *Aphasiology, 13*(1), 79-87.
- Ardila, A. (2008). On the evolutionary origins of executive functions. *Brain and Cognition, 68*(1), 92-99.
- Ardila, A. (2014). Aphasia Handbook. Miami, FL: Florida International University. <https://aalfredoardila.files.wordpress.com/2013/07/ardila-a-2014-aphasia-handbook-miami-fl-florida-international-university2.pdf>. Accessed 01/05/2015
- Ardila, A., Bernal, B., & Rosselli, M. (2014). Participation of the insula in language revisited: A meta-analytic connectivity study. *Journal of Neurolinguistics, 29*, 31-41.
- Ardila, A., Bernal, B., & Rosselli, M. (2015). Language and visual perception associations: Meta-analytic connectivity modeling of Brodmann area 37. *Behavioral Neurology*.
- Basho, S., Palmer, E. D., Rubio, M. A., Wulfeck, B., & Müller, R. A. (2007). Effects of generation mode in fMRI adaptations of semantic fluency: Paced production and overt speech. *Neuropsychologia, 45*(8), 1697-1706.
- *Bedny, M., & Thompson-Schill, S. L. (2006). Neuroanatomically separable effects of imageability and grammatical class during single-word comprehension. *Brain and Language, 98*(2), 127-139.
- Benson, D. F., & Ardila, A. (1996). *Aphasia: A clinical perspective*. New York: Oxford University Press.
- Berthier, M. L. (2000). *Transcortical aphasias*. Psychology Press.
- Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience, 9*(2), 141.
- *Booth, J. R., Burman, D. D., Meyer, J. R., Gitelman, D. R., Parrish, T. B., & Mesulam, M. (2002). Modality independence of word comprehension. *Human Brain Mapping, 16*(4), 251-261.
- Brainmap.org. <https://www.brainmap.org/>. Accessed 10/12/2015
- Brodmann's Interactive Atlas. <http://www.fmriconsulting.com/brodmann/BA5.html>. Accessed 10/12/2014
- Chayer, C., & Freedman, M. (2001). Frontal lobe functions. *Current Neurology and Neuroscience Reports, 1*, 547-552.
- Collins, M. L. (2001). *Handbook of developmental cognitive neuroscience*. Cambridge: MIT Press.
- Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology, 50*, 873-880.
- Damasio, A., & Anderson, S. W. (2003). The frontal lobes. In K. M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (4th ed., pp. 404-446). New York: Oxford University Press.
- *Damasio, H., Grabowski, T. J., Tranel, D., Ponto, L. L., Hichwa, R. D., & Damasio, A. R. (2001). Neural correlates of naming actions and of naming spatial relations. *Neuroimage, 13*(6), 1053-1064.
- *Davis, M. H., Meunier, F., & Marslen-Wilson, W. D. (2004). Neural responses to morphological, syntactic, and semantic properties of single words: An fMRI study. *Brain and Language, 89*(3), 439-449.
- *Dapretto, M., & Bookheimer, S. Y. (1999). Form and content: Dissociating syntax and semantics in sentence comprehension. *Neuron, 24*(2), 427-432.
- De Carli, D., Garreffa, G., Colonnese, C., Giulietti, G., Labruna, L., Briselli, E., Ken, S., Macri, M.A., & Maraviglia, B. (2007). Identification of activated regions during a language task. *Magnetic Resonance Imaging, 25*(6), 933-938.
- *Desai, R., Conant, L. L., Waldron, E., & Binder, J. R. (2006). fMRI of past tense processing: The effects of phonological complexity and task difficulty. *Journal of Cognitive Neuroscience, 18*(2), 278-297.
- *Devlin, J., Matthews, P., & Rushworth, M. (2003). Semantic processing in the left inferior prefrontal cortex: A combined functional magnetic resonance imaging and transcranial magnetic stimulation study. *Journal of Cognitive Neuroscience, 15*(1), 71-84.
- Duffau, H., Gatignol, P., Moritz-Gasser, S., & Mandonnet, E. (2009). Is the left uncinate fasciculus essential for language? *Journal of Neurology, 256*(3), 382-389.
- Fox, P. T., Ingham, R. J., Ingham, J. C., Zamarripa, F., Xiong, J. H., & Lancaster, J. L. (2000). Brain correlates of stuttering and syllable production: A PET performance-correlation analysis. *Brain, 123*(10), 1985-2004.
- Fuster, J. M. (2001). The prefrontal cortex-an update: Time is of the essence. *Neuron, 30*, 319-333.
- Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neuropsychology, 31*, 373-385.
- Fuster, J. M. (2008). *The prefrontal cortex* (4th ed.). Boston: Academic Press.
- Goldberg, E. (2001). *The executive brain*. New York: Oxford University Press.
- Grafman, J. (2006). Human prefrontal cortex: Processes and representations. In J. Risberg & J. Grafman (Eds.), *The frontal lobes: Development, function and pathology* (pp. 69-91). Cambridge, MA: Cambridge University Press.
- Grodzinsky, Y., & Amunts, K. (Eds.) (2006). *Broca's region*. New York: Oxford University Press.

- Jackson III, O., & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage*, 21(1), 456-462.
- Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*, 17(3), 213-233.
- Heim, S., Opitz, B., Müller, K., & Friederici, A. D. (2003). Phonological processing during language production: fMRI evidence for a shared production-comprehension network. *Cognitive Brain Research*, 16(2), 285-296.
- Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition*, 92(1), 67-99.
- Inui, T., Otsu, Y., Tanaka, S., Okada, T., Nishizawa, S., & Konishi, J. (1998). A functional MRI analysis of comprehension processes of Japanese sentences. *NeuroReport*, 9(14), 3325-3328.
- *Jackson, O., & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *Neuroimage*, 21(1), 456-462.
- *Kang, A. M., Constable, R. T., Gore, J. C., & Avrutin, S. (1999). An event-related fMRI study of implicit phrase-level syntactic and semantic processing. *Neuroimage*, 10(5), 555-561.
- Koziol, L. F., & Budding, D. E. (2009). *Subcortical structures and cognition*. New York: Springer.
- Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., Turkeltaub, P. E., Kochunov, P., & Fox, P. T. (2005). ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping*, 25, 155-164.
- *Longe, O., Randall, B., Stamatakis, E. A., & Tyler, L. (2007). Grammatical categories in the brain: The role of morphological structure. *Cerebral Cortex*, 17(8), 1812-1820.
- Luria, A. R. (1980). *Higher cortical functions in man* (2nd ed.). New York: Basic.
- Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., & Duffau, H. (2007). Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain*, 130(3), 623-629.
- Martino, J., Brogna, C., Robles, S. G., Vergani, F., & Duffau, H. (2010). Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. *Cortex*, 46(5), 691-699.
- McDermott, K. B., Petersen, S. E., Watson, J. M., & Ojemann, J. G. (2003). A procedure for identifying regions preferentially activated by attention to semantic and phonological relations using functional magnetic resonance imaging. *Neuropsychologia*, 41(3), 293-303.
- Mesulam, M. M. (1986). Frontal cortex and behavior. *Annals of Neurology*, 19, 320-325.
- Mesulam, M. M. (2002). The human frontal lobes: Transcending the default mode through contingent encoding. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 8-31). New York: Oxford.
- *Peck, K. K., Wierenga, C. E., Moore, A. B., Maher, L. M., Gopinath, K., Gaiefsky, M., ... & Crosson, B. (2004). Comparison of baseline conditions to investigate syntactic production using functional magnetic resonance imaging. *NeuroImage*, 23(1), 104-110.
- *Poldrack, R., Temple, E., Protopapas, A., Nagarajan, S., Tallal, P., Merzenich, M., & Gabrieli, J. (2001). Relations between the neural bases of dynamic auditory processing and phonological processing: Evidence from fMRI. *Journal of Cognitive Neuroscience*, 13(5), 687-697.
- Price, C. J., Green, D. W., & Von Studnitz, R. (1999). A functional imaging study of translation and language switching. *Brain*, 122(12), 2221-2235.
- Robinson, J. L., Laird, A. R., Glahn, D. C., Lovallo, W. R., & Fox, P. T. (2010). Meta-analytic connectivity modeling: Delineating the functional connectivity of the human amygdala. *Human Brain Mapping*, 31(2), 173-184.
- Ross, E. D. (1981). The aprosodias: Functional-anatomical organization of the affective components of language in the right hemisphere. *Archives of Neurology*, 140, 695-710.
- *Rosen, H. J., Petersen, S. E., Linenweber, M. R., Snyder, A. Z., White, D. A., Chapman, L., & Corbetta, M. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology*, 55(12), 1883-1894.
- *Rowan, A., Liégeois, F., Vargha-Khadem, F., Gadian, D., Connelly, A., & Baldeweg, T. (2004). Cortical lateralization during verb generation: A combined ERP and fMRI study. *Neuroimage*, 22(2), 665-675.
- *Sabsevitz, D. S., Medler, D. A., Seidenberg, M., & Binder, J. R. (2005). Modulation of the semantic system by word imageability. *Neuroimage*, 27(1), 188-200.
- *Schlösser, R., Hutchinson, M., Joseffer, S., Rusinek, H., Saarimaki, A., Stevenson, J., Dewey, S. L., & Brodie, J. D. (1998). Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *Journal of Neurology, Neurosurgery & Psychiatry*, 64(4), 492-498.
- Shammí, P., & Stuss, D. T. (1999). Humour appreciation: A role of the right frontal lobe. *Brain*, 122(4), 657-666.
- *Sharp, D. J., Awad, M., Warren, J. E., Wise, R. J., Vigliocco, G., & Scott, S. K. (2010). The neural response to changing semantic and perceptual complexity during language processing. *Human Brain Mapping*, 31(3), 365-377.
- Shuster, L. I., & Lemieux, S. K. (2005). An fMRI investigation of covertly and overtly produced mono- and multisyllabic words. *Brain and Language*, 93(1), 20-31.
- *Simmons, W. K., Hamann, S. B., Harenski, C. L., Hu, X. P., & Barsalou, L. W. (2008). fMRI evidence for word association and situated simulation in conceptual processing. *Journal of Physiology-Paris*, 102(1), 106-119.
- Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobe: A conceptual view. *Psychological Research*, 63, 289-298.
- Stuss, D. T., & Alexander, M. P. (2007). Is there a dysexecutive syndrome? *Philosophical Transactions of the Royal Society*, 362, 901-915.
- Stuss, D. T., & Knight, R. T. (2002). *Principles of frontal lobe function*. New York: Oxford University Press.
- *Tan, L. H., Spinks, J. A., Feng, C. M., Siok, W. T., Perfetti, C. A., Xiong, J., & Gao, J. H. (2003). Neural systems of second language reading are shaped by native language. *Human Brain Mapping*, 18(3), 158-166.
- Tonkonogy, J., & Puente, A. (2009). *Localization of clinical syndromes in neuropsychology and neuroscience*. New York: Springer Publishing Company.
- Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. *NeuroImage*, 16(3, Part 1), 765.
- Turken, U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience*, 5, 1.
- Wang, S., Zhu, Z., Zhang, J. X., Wang, Z., Xiao, Z., Xiang, H., & Chen, H. C. (2008). Broca's area plays a role in syntactic processing during Chinese reading comprehension. *Neuropsychologia*, 46(5), 1371-1378.
- Wernicke, C. (1874). *Der Aphasische Symptomencomplex*. Breslau: Cohn & Weigert.