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Participation of the insula in language revisited: A meta-analytic connectivity study

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Despite the insula's location in the epicenter of the human language area, its specific role in language is not sufficiently understood. The left insula has been related to a diversity of speech/language functions, including articulatory planning, language repetition ability, and phonological recognition. To further our understanding of the role of the insula in language, a meta-analytic connectivity study using the Activation Likelihood Estimation (ALE) technique was developed. By means of the BrainMap functional database, 26 papers corresponding to 39 paradigms, and including 522 participants were selected. Thirteen different activation clusters were found; insula connections included not only areas involved in language production (such as the Broca's area) and language understanding (such as the Wernicke's area), but also areas involved in language repetition (such as the supramarginal gyrus) and other linguistic functions, such as BA9 in the left prefrontal lobe (involved in complex language processes) and BA37 (involved in lexico-semantic associations). In conclusion, the insula represents a core area in language processing, as it was suggested during the 19th century.

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1. Introduction

The insula (or Island of Reil) is a complex and not completely understood brain area. Its potential participation in language has been a topic of controversy since the 19th century (Freud, 1891; Wernicke, 1874/1970), even though currently it seems evident that it plays a crucial role in language processing (Price, 2010). The anterior segment of the insula extends to and interfaces with Broca's area while its posterior elements adjoin Wernicke's area (Flynn, Benson, & Ardila, 1999). The left insula is notably larger than the right in most humans (Greve et al., 2013; Mesulam & Mufson, 1985). Both the asymmetry and the location in the epicenter of the human language area (Benson & Ardila, 1996; Dejerine, 1914; Luria, 1976) suggest that the insula may be active in language processes. However, few papers have been specifically devoted to the analysis of the role of the insula in language (e.g., Ackermann & Riecker, 2004; Ardila, 1999; Ardila, Benson, & Flynn, 1997).

Since Wernicke (1874), the insula has frequently been implicated in the "major aphasic syndromes": Broca's aphasia, conduction aphasia, and Wernicke's aphasia. In fact, Wernicke (1874) directly related insula damage with conduction aphasia. Involvement of the anterior part of the insula in Broca's aphasia was noted by Bernheim (1900) and Dejerine (1914) at the beginning of the 20th century. Furthermore, Liepmann and Storck (1902) associated the word-deafness component of Wernicke's aphasia with posterior insula pathology.

Pathology involving only the insular cortex and immediate sub-cortical structures, has been rarely reported however. Alexander, Benson, and Stuss (1989) presented two cases of pathology limited to the left insula and subjacent extreme-external capsules. Aphasia with mildly paraphasic production and agraphia was noted in both cases. Nielsen and Friedman (1942) reported several autopsy findings illustrating the association between left insula damage and aphasia. They noted, however, from their own cases and others in the literature, that a similar language syndrome followed isolated extreme capsule damage and postulated that insular damage without extreme capsule involvement would not produce aphasia. Habib et al. (1995) reported a case of bilateral insular damage, extending to a small part of the striatum on the left side, and to the temporal pole on the right. The patient presented mutism for about one month, did not respond to any auditory stimuli, and made no effort to communicate.

It is noteworthy that mutism has been frequently observed in individuals who suffered from insular damage. Transient mutism is found in cases of left inferior motor cortex damage extending to the insula (Alexander et al., 1989; Schiff, Alexander, Naeser, & Galaburda, 1983), whereas lasting mutism appears to be associated with bilateral lesions of the frontal operculum and anterior insula (Cappa, Guidotti, Papagno, & Vignolo, 1987; Groswaser, Korn, Groswaser-Reider, & Solzi, 1988; Pineda & Ardila, 1992; Sussman, Gur, Gur, & O'Connor, 1983). Alexander et al. (1989) suggested that left cortical and subcortical opercular lesions frequently result in a total speech loss associated with a right hemiparesis. Shuren (1993) described a patient who developed impaired speech initiation as a result of a left anterior insular infarct and suggested that anterior insular lesions in the left hemisphere could impair speech initiation. A possible interactive role of the left insula in speech initiation and language motivation could thus be conjectured (Ardila et al., 1997).

Dronkers (1996) showed that the left precentral gyrus of the insula is involved in motor planning of speech. Twenty-five stroke patients with a disorder in planning of articulatory movements (apraxia of speech), were compared with 19 individuals without such deficits. It was found that all patients with articulatory planning impairments presented lesions including the anterior insula. This area was completely spared in all patients without these articulatory defects. It was concluded that anterior insula represents a crucial brain area in motor planning and organization of speech. Verbal articulatory disruptions in some cases may be so severe as to result in mutism (Alexander et al., 1989; Pineda & Ardila, 1992).

Contemporary neuroimaging technique studies have supported the hypothesis regarding an active involvement of the insula in linguistic processes. Activation of the insula has been demonstrated in a diversity of verbal tests, including word generation (Baker, Frith, & Dolan, 1997; Bohland & Guenther, 2006; Gurd et al., 2002; Kemeny, Ye, Birn, & Braun, 2005; McCarthy, Blamire, Rothman, Gruetter, & Shulman, 1993; Pihlajamaki et al., 2000; Rowan et al., 2004; Voets et al., 2006), naming (Berlingeri et al., 2008; Damasio et al., 2001; Price, Moore, Humphreys, Frackowiak, & Friston, 1996), and phonological discrimination (Booth et al., 2002; Rumsey et al. 1997; Tyler, Stamatakis, Post, Randall, & Marslen-Wilson, 2005) (see Table 1). The insula has also been related to auditory processing (Bamiou, Musiek, & Luxon, 2003). Bates et al. (2003) analyzed the speech fluency and language comprehension of 101 patients with a left hemisphere stroke using voxel-based lesion symptom mapping the authors identified the insula as a crucial area in language; they observed that lesions involving the insula had a significant impact in verbal fluency.

These findings support the conclusion that the insula significantly participates in language. Furthermore, they suggest that the insula is not be involved in a single linguistic process, but simultaneously in several verbal processes. The anterior portion of the insula appears to be involved in the organization and planning of language articulation, and language initiation; while the middle and posterior portions appear to be involved with lexical knowledge, word retrieval, language understanding, and phonological discrimination.

Other studies have also suggested that the insula is involved in second language learning in bilinguals (e.g., Archila-Suerte, Zevin, Ramos, & Hernandez, 2013; Buchweitz, Shinkareva, Mason, Mitchell, & Just, 2012; Chan et al., 2008; Hernandez, 2009; Saur et al., 2009; Veroude, Norris, Shumskaya, Gullberg, & Indefrey, 2010). Chee, Soon, Lee, and Pallier (2004) analyzed the brain activity English/Chinese bilinguals. They observed that the left insula showed greater activation in equal

Table 1
Primary studies of language-related paradigms included in the meta-analysis (26 studies; 39 paradigms; 522 subjects).

Publication	Paradigm	*n*	Foci
Booth et al., 2002	Semantic monitor/discrimination	13	15
	Phonological discrimination	13	7
Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002	Phonological discrimination	10	7
Michael, Keller, Carpenter, & Just, 2001	Semantic monitor/discrimination	9	18
Palmer et al., 2001	Word stem completion	10	26
Shaywitz et al., 1995	Word generation	9	15
	Word generation	9	11
Dapretto & Bookheimer, 1999	Semantic monitor/discrimination	8	8
Schlosser et al., 1998	Word generation	6	11
Binder et al., 2003	Semantic monitor/discrimination	24	9
Poldrack et al., 2001	Semantic monitor/discrimination	8	5
	Semantic monitor/discrimination	8	5
Riecker, Ackermann, Wildgruber, Dogil, & Grodd, 2000	Recitation/repetition	18	6
Rowan et al., 2004	Word generation	10	13
Pihlajamaki et al., 2000	Word generation	14	9
Gurd et al., 2002	Word generation	11	8
Kemeny et al., 2005	Word generation	6	12
Voets et al., 2006	Word generation	12	14
Bohland & Guenther, 2006	Recitation/repetition	13	18
	Recitation/repetition	13	54
Seghier, Lazeyras, Pegna, Annoni, & Khateb, 2008	Semantic monitor/discrimination	50	10
Thompson et al., 2007	Semantic monitor/discrimination	17	25
	Semantic monitor/discrimination	17	28
	Semantic monitor/discrimination	17	31
Haller, Radue, Erb, Grodd, & Kircher, 2005	Word generation	15	9
	Word generation	15	7
Damasio et al., 2001	Naming	20	5
	Naming	20	4
Simmons, Hamann, Harenski, Hu, & Barsalou, 2008	Word generation	10	32
	Word generation	10	23
Sharp et al., 2010	Semantic monitor/discrimination	12	13
Davis, Meunier, & Marslen-Wilson, 2008	Complex noun vs. simple noun	12	2
Longe, Randall, Stamatakis, & Tyler, 2007	Semantic monitor/discrimination	12	14
	Semantic monitor/discrimination	12	13
	Semantic monitor/discrimination	12	4
	Semantic monitor/discrimination	12	2
Berlingeri et al., 2008	Naming	12	14
Tyler et al., 2005	Phonological discrimination	18	9
	Phonological discrimination	18	7

bilinguals. Unequal bilinguals showed greater task-related deactivation in the anterior medial frontal region and greater anterior cingulate activation. These authors suggested that left insula activation can be regarded a marker for language attainment in bilinguals. Similar results were reported by Gandour et al. (2007).

The insula has also been related to the learning of grammar. Yang and Li (2012) analyzed the neural correlates of explicit and implicit learning of artificial grammar sequences. Using effective connectivity analyses of functional magnetic resonance imaging (fMRI) they found that different brain systems support these two types of learning: both activate some specific cortical and subcortical brain areas, but explicit learning is based in a circuit that includes the insula as a key mediator; implicit learning on the other hand activates a frontal-striatal circuit. There is no question that the insula plays a crucial role in grammar learning.

It is noteworthy that the insula possesses not only contralateral motor and sensory representation but also ipsilateral motor and sensory connections (Flynn et al., 1999). Connections have been described between the insula and the orbital cortex, frontal operculum, lateral premotor cortex, ventral granular cortex, and medial area 6 in the frontal lobe. The insula has been found to also connect with the temporal pole and the superior temporal sulcus. Significant projections to the cingulate gyrus, amygdaloid nucleus, perirhinal cortex, entorhinal and periamygdaloid cortex have been observed (Augustine, 1996; Flynn et al., 1999). The insula in consequence maintains a complex system of interconnections not only with classical cortical language regions in the temporal and frontal lobe, but with a variety of limbic structures as well, including the cingulate gyrus and the perirhinal and entorhinal cortex.

Bressler and Menon (2010) have emphasized that cognition results from the dynamic interactions of distributed brain areas operating in large-scale networks. They specifically refer to a "salience network" involved in monitoring the salience of external inputs and internal brain events. This salience network is proposed to be anchored in anterior insular and dorsal anterior cingulate cortices.

The analysis of the functional connectivity of the insula becomes most important in understanding its real contribution to the language brain system. Currently, there are several techniques that can potentially demonstrate brain networks. These techniques are grouped under the term "brain connectivity". Recently, a new alternative to study brain connectivity has been proposed by Robinson, Laird, Glahn, Lovallo, and Fox (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, the insula), 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 coactivations that can be statistically analyzed for significant commonality. As a final step, Activation Likelihood Estimation (ALE) (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002) that can be performed utilizing GingerALE, another software also provided by BrainMap, generating 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 insula in language a meta-analytic connectivity utilizing MACM on the participation of the insula in language was developed. It was hypothesized that the left insula participated in different brain language circuits associated with different language functions.

2. Materials and methods

The DataBase of Brainmap (brainMap.org) was accessed utilizing Sleuth 2.2 on October 10, 2013. Sleuth is the software provided by BrainMap to query its database. The meta-analysis was intended to assess the network of coactivations in which the insula is involved.

The search conditions were: (1) studies reporting insula activation; (2) studies using fMRI; (3) context: normal subjects; (4) activations: activation only; (5) handedness: right-handed subjects; (6) age 20–60 years; (7) domain: cognition, subtype: language.

(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 5 × 7 insets of transversal fusioned 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.

3. Results

Twenty-six papers corresponding to 39 experimental conditions with a total of 522 subjects were selected (subjects participating in two different experiments were counted as two subjects) (Table 1).

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

Region (BA)	*x*	*y*	*z*	ALE	Volume (mm^3)
Cluster #1					
L claustrum	−34	16	2	0.037919	15,504
L insula (13)	−32	18	8	0.037371	
L inferior frontal gyrus (9)	−44	14	26	0.036325	
L inferior frontal gyrus (9)	−44	8	20	0.03527	
L inferior frontal gyrus (9)	−42	4	26	0.034871	
L inferior frontal gyrus (44)	−54	8	20	0.021423	
Cluster #2					
L cingulate gyrus (24)	−2	10	46	0.047008	6672
L medial frontal gyrus (6)	−6	0	56	0.03508	
R cingulated gyrus (32)	4	16	40	0.031888	
Cluster #3					
R claustrum	34	20	0	0.045935	3672
R insula (13)	44	18	2	0.030737	
Cluster #4					
L parietal lobe precuneus (7)	−24	−66	42	0.029916	2720
L superior parietal (7)	−28	−58	46	0.028488	
Cluster #5					
L anterior culmen	−38	−44	−22	0.025062	2024
L anterior culmen	−34	−42	−23	0.023365	
L fusiform gyrus (37)	−42	−56	−18	0.022605	
Cluster #6					
L middle temporal gyrus (22)	−54	−48	4	0.026263	1872
L superior temporal gyrus (22)	−48	−40	4	0.024667	
Cluster #7					
L supramarginal gyrus (40)	−44	−40	42	0.022375	1336
L inferior parietal lobe (40)	−38	−48	48	0.015987	
L inferior parietal lobe (40)	−38	−30	40	0.015765	
Cluster #8					
L frontal precentral (4)	−50	−10	44	0.024215	800
Cluster #9					
R thalamus medial dorsal nucleus.	10	−16	6	0.022084	488
Cluster #10					
L inferior parietal lobe (40)	−54	−24	36	0.021431	400
Cluster #11					
R superior temporal gyrus (41)	46	−32	6	0.020212	320
Cluster #12					
L fusiform occipital (19)	−24	−88	−8	0.020601	304
Cluster #13					
R cerebellum posterior lobe	28	−64	−24	0.017119	248

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

The first cluster includes the claustrum (that is the insular subcortical gray matter); but this focus extends not only subcortically, but also anteriorly toward the BA9 (middle frontal gyrus in the prefrontal cortex, involved in complex language processes, including the use of verbal strategies in executive functions; see: Brodmann's Interactive Atlas) and BA44 (Broca's area, involved in language production, grammar, and language fluency and sequencing; Ardila, 2012; Grodzinsky & Amunts, 2006).

The second cluster includes both anterior cingulate gyrus (involved in motor organization – motor preparation/planning, cognitive/motor inhibition – and language initiative), and BA6 (medial frontal gyrus); BA6 includes the supplementary motor area (SMA), clearly involved in language initiation and maintenance of voluntary speech production (Ardila, 2012). Thus, this second cluster suggests an involvement of the insula in a brain circuit controlling verbal initiative and maintenance of speech production.

Cluster #3 includes the right insula and the insular subcortical gray matter (claustrum) and indicates an integrated activity of both, the left and right insula. Cluster #4 refers to left BA7 (superior parietal lobe); this brain area is involved in ideomotor praxis (Tonkonogy & Puente, 2009), motor imagery (Solodkin, Hlustik, Chen, & Small, 2004; Stephan et al., 1995), motor learning (Tonkonogy & Puente, 2009), language processing (Seghier et al., 2004) and, temporal context recognition (Zorrilla, Aguirre, Zarahn, Cannon, & D'Esposito, 1996); thus, seemingly, the insula is also involved in the language system related to some contextual and motor learning aspects of speech.

The following cluster (#5) involves BA37 (posterior inferior temporal gyrus, middle temporal gyrus, and fusiform gyrus) and the cerebellar culmen; however, considering that BA37 is exactly above the culmen, most likely this activation refers to BA37, and so cluster #5 simply includes the left BA37. It is

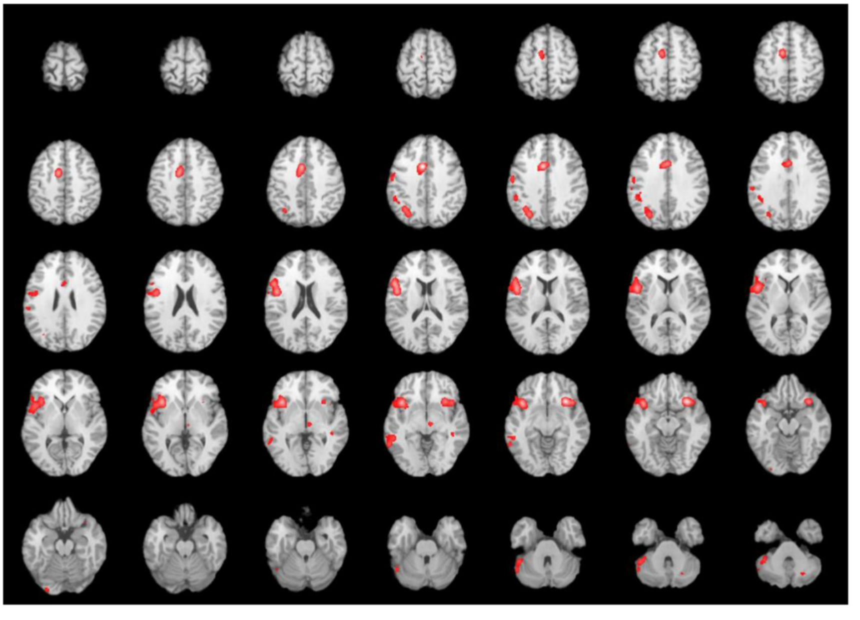

Fig. 1. Brain network of the insula. ALE results were overlaid on a T1 MRI template. Left hemisphere appears in the left side of the insets (neurological convention). Major foci of activation are situated at the left insula/BA9 (Middle frontal gyrus)/BA44 (Broca's area, pars opercularis); left cingulate gyrus/SMA; right insula; left BA7 (superior parietal lobe); left BA37 (fusiform gyrus); left BA22 (superior middle temporal gyrus); left BA40 (supramarginal gyrus, inferior parietal lobe); (BA4) left precental gyrus; medial dorsal nucleus of the thalamus; BA40 (inferior parietal lobe); right BA41 (superior temporal gyrus, primary auditory cortex); BA19 (left fusiform occipital gyrus); right posterior lobe of the cerebellum.

well known that BA37 is involved in lexico-semantic associations (i.e., associating words with visual percepts) (see Brodmann's Interactive Atlas); clinical observations have demonstrated that damage in the left BA37 is associated with significant word-finding difficulties (anomia) (e.g., Antonucci, Beeson, Labiner, & Rapcsak, 2008; Luria, 1976; Raymer et al., 1997), impaired naming of pictures, significant amount of semantic paraphasias, and relatively preserved word comprehension (Foundas, Daniels, & Vasterling, 1998; Raymer et al., 1997).

The following two clusters (#6 and #7) refer to two areas traditionally involved in language: left BA22 (superior temporal gyrus – part of Wernicke's area), and left BA40 (supramarginal gyrus). The first one is considered to be a crucial area in language understanding, whereas the second one has been related to language repetition (Tonkonogy & Puente, 2009), and semantic processing (Chou et al., 2006).

The next activation clusters (#8 and 9) include the left BA4 (Primary motor cortex – precentral gyrus) and the medial dorsal nucleus of the thalamus, which receives inputs from the hypothalamus and projects to the pre-frontal cortex; it has been related to attention and memory. Although a direct relation with language is not evident, clusters #8 and cluster #9 may be contributing to the motor aspects of speech and to the attention control of language. Cluster #10 on the other hand, is similar to cluster #7 and includes BA #40 (inferior parietal lobe).

The last three clusters (particularly smaller, with 300 mm^3 or less) includes the BA41 (primary auditory cortex – Heschl's gyrus), BA19 (secondary visual cortex – Inferior occipital or fusiform gyrus) and the posterior lobe of the cerebellum, that indeed could be an extension of the fusiform gyrus activation; the activation of these clusters may suggest some participation of the insula in language recognition and visual associations.

Fig. 2 illustrates the insula connections in the left hemisphere.

4. Discussion

The current meta-analytic connectivity study reveals the participation of the left insula in a complex brain network involved in different aspects of language. Significant connections with left Broca's area

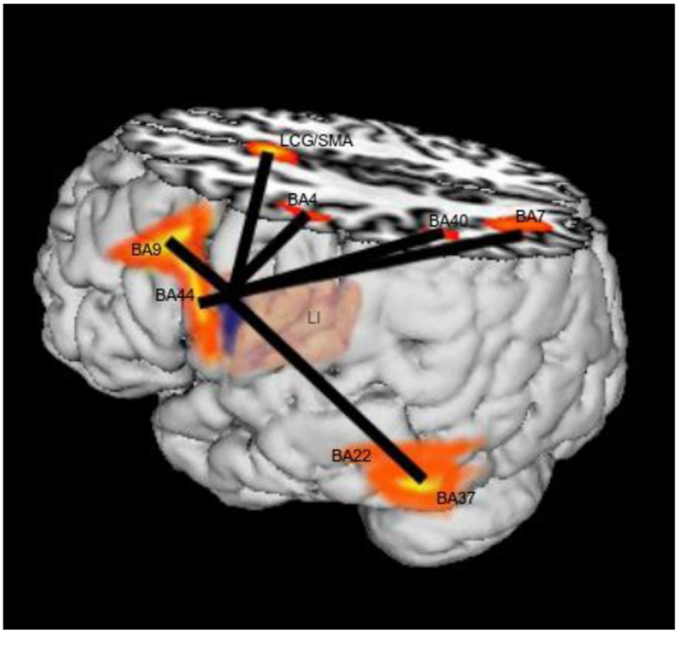

Fig. 2. Artist's rendition of the insula connections (left hemisphere). The position of the insula (deep in the brain) is shown. The figure illustrates only the connections, because the direction and sequence of activation cannot be determined. LI: Left insula; LCG/SMA: left cingulate gyrus and supplementary motor area; BA: Brodmann Area.

(BA44) and the left middle frontal gyrus (area 9) clearly support attributing involvement of the insula in language production and complex language organization. This observation is congruent with the report that the anterior insula participates in motor planning of speech (Dronkers, 1996); it is well known that speech apraxia (that is precisely a defect in motor planning of speech) represents one of the two fundamental deficits in Broca's aphasia (Benson & Ardila, 1996; Luria, 1976); the other one is agrammatism, more specifically related to Broca's area, which is clearly connected with the left insula.

The significant connections between the insula on one hand, and the cingulate gyrus and the SMA on the other, represents further support for the observation that the insula damage can be associated with impairments in the ability to initiate and maintain voluntary speech production and mutism (Alexander et al., 1989; Habib et al., 1995; Schiff et al., 1983). It has been well established that mesial frontal damage can be associated with mutism, and in severe cases, with the akinetic mutism (Ross & Stewart, 1981). Moreover, the insula also appears to be involved in some contextual and motor learning aspects of speech.

The association of the insula with BA37 (posterior inferior temporal gyrus, middle temporal gyrus, and fusiform gyrus) refers to a different level of language: naming and language understanding. This assumption is further supported by the observation that the insula is also significantly connected with Wernicke's area (BA22; superior temporal gyrus). The association with left BA40 (supramarginal gyrus) suggests that the insula may be involved in circuits related to language repetition, taking into consideration that language repetition defects associated with conduction aphasia are observed in BA40 lesions (Damasio & Damasio, 1980). It is noteworthy that insula damage can result in conduction aphasia (Damasio & Damasio, 1980); and historically, the first case of conduction aphasia was reported in a patient with insular pathology (Wernicke, 1874).

Clinical/anatomical correlations have suggested that the insula may be involved in multiple language functions, including language production, language understanding and language repetition (for a review of these clinical/anatomical correlations see: Ardila, 1999). In fact, left insula pathology has been related to Broca's aphasia (e.g., speech apraxia), conduction aphasia (e.g., language repetition defects), and also Wernicke's aphasia (e.g., impairments in language understanding). This observation makes the insula a most central area in language processing, as was suggested during the 19th (for a review of this question, see Freud, 1891). Unfortunately, the interest in the potential involvement of the insula in language disappeared for almost one century. This lack of interest in the potential role of the insula in language may be related to the concept of "language zone" in the brain suggested by Dejerine (1914); According to Dejerine, this language zone (or language area) includes the left frontal (posterior part of the foot of F3, the frontal operculum, and the immediate surrounding zone, including the foot of F2, and *probably* extending to the anterior insula), temporal (encompassing the posterior first and second temporal gyri), and parietal (the angular gyrus) areas. The concept of language area was accepted by most researchers in the area, and the insula was neglected during most of the 20th century.

Contemporary neuroimagining techniques, however, support the conclusion that the insula represents a core area in language processing, involved in a diversity of language functions including both comprehension and production; and in lexical and grammatical learning; and even in second language acquisition.

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