Published in final edited form as:

Brain Lang. 2012 November ; 123(2): 125–130. doi:10.1016/j.bandl.2012.08.007.

Re-establishing Broca's Initial Findings

Jessica D. Richardson^a, Paul Fillmore^a, Chris Rorden^b, Leonard LaPointe^c, Julius Fridriksson^a

^aDepartment of Communication Sciences and Disorders, University of South Carolina, Columbia, SC 29208

^bDepartment of Psychology, University of South Carolina, Columbia, SC 29208

^cDepartment of Communication Sciences and Disorders, Florida State University, Tallahassee, FL 32306

Abstract

The importance of the left inferior pre-frontal cortex (LIPC) for speech production was first popularized by Paul Broca, providing a cornerstone of behavioral neurology and laying the foundation for future research examining brain-behavior relationships. Although Broca's findings were rigorously challenged, comprehensive contradictory evidence was not published until 130 years later. This evidence suggested that damage to left anterior insula was actually the best predictor of motor speech impairment. Using high-resolution structural magnetic resonance imaging (MRI) in patients with chronic stroke, we reveal that LIPC involvement more accurately predicts acquired motor speech impairment than insula damage. Perfusion-weighted MRI provides complementary evidence, highlighting how damage to left inferior pre-frontal gyrus often includes insula involvement, and vice versa. Our findings suggest that Broca's initial conclusions associating acquired motor speech impairment with LIPC damage remain valid nearly 150 years after his initial report on this issue.

Keywords

aphasia; apraxia; cerebral blood flow; Broca; insula; lesion; MRI; PASL; perfusion; pre-frontal cortex

1. Introduction

In 1861, Broca described Leborgne, a patient with non-fluent speech and damage to left inferior pre-frontal cortex (LIPC) and surrounding regions. After having examined 20 or so additional patients with impaired speech, most having LIPC involvement, Broca concluded

Corresponding Author: Jessica D. Richardson, PhD, Research Assistant Professor, Department of Communication Sciences & Disorders, University of South Carolina, Discovery 1, 915 Greene Street, Columbia, SC 29208, j.d.richardson@sc.edu, Phone: (803) 777-5049, Fax: (803) 777-4750.

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that this region, now known as Broca's area (defined here as the left *pars triangularis* [LIPCpt] and *pars opercularis* [LIPCpo]), was the cortical seat of motor speech (Broca, 1865). Broca's presentations were milestones in the history of the neuroscience of speech, language and the brain, but they were only more defined echoes of assertions of cortical localization of function that had preceded him (LaPointe, in press). The French physicians Bouillaud and Aubertin had previously advanced notions of the primacy of the left cerebral hemisphere and its role in human speech. Shortly after attending a presentation by Aubertin addressing speech cessation (Aubertin, 1861), Broca presented clinicopathological evidence of damaged cortical loci that were presumed to account for the speech-language difficulty of his two classic patients, Leborgne and Lelong (LaPointe, in press).

Broca's 1861 presentation is considered the cornerstone of modern behavioral neurology and the foundation for more sophisticated research examining brain-behavior relationships (Ryalls & Lecours, 1996). Broca's original work (Broca, 1861, 1863) revealed that his descriptions of Leborgne's speech were much more akin to today's understanding of apraxia of speech (AOS), a motor speech impairment, rather than aphasia, a language impairment that is more commonly associated with Broca (e.g., Broca's aphasia). In Broca's (1861) words:

"What is missing in these patients is only the faculty to articulate the words; they hear and understand all that is said to them, they have all their intelligence and they emit easily vocal sounds. What is lost is therefore not the faculty of language, is not the memory of the words nor is it the action of nerves and muscles of phonation and articulation, but something else ... the faculty to coordinate the movements which belong to the articulate language, or simpler, it is the faculty of articulate language." (p. 334)

Although Broca's findings were rigorously challenged, comprehensive contradictory evidence was not published until 130 years later (Dronkers, 1996). In a seminal study, Dronkers (1996) revealed that, compared to Broca's area involvement, localized damage to left anterior insula (LAIns) is a better predictor of impaired motor speech in chronic stroke. In this study, patient-by-patient lesion demarcations were made for patients with and without AOS on a standard brain template based on clinical computerized tomography (CT) or magnetic resonance imaging (MRI) scans. The greatest lesion overlap among AOS patients was found in LAIns, with less involvement of Broca's area. Damage to LAIns was not noted for patients without AOS. Dronker's conclusions not only contradicted Broca's initial findings but, more importantly, suggested that LAIns is the crucial area subserving motor speech processing. In a later study, Ogar et al. (2006) again used the lesion overlap method to demonstrate that the LAIns (specifically the superior precentral gyrus of the insula) was completely spared in patients without AOS.

The primary weakness of utilizing the lesion overlap approach to identify cortical areas crucial for a specific behavior lies within the interpretation of results, as the area of greatest overlap could be more related to the common sites of brain damage characteristic of the population under study (e.g., persons with left hemisphere stroke) and not necessarily associated with the discrete behavior (Rorden & Karnath, 2004). Further, Hillis et al. (2004) pointed out that relying on structural images alone to infer relationships between lesion

location and impaired speech may be fundamentally flawed, since lesions that affect the insula are likely to cause hypoperfusion of Broca's area. Subsequently, Broca's area may be functionally lesioned in cases where structural scans only reveal damage restricted to the insula. To investigate this possibility, Hillis' (2004) group related clinical ratings of structural or functional cortical involvement visible on diffusion- and perfusion-weighted MRI, restricting their search to plausible regions of interest, to presence or absence of AOS in a large sample of acute patients with left hemisphere stroke. Crucially, they concluded that structural damage or cortical hypoperfusion of Broca's area is the most reliable predictor of AOS.

Building on the work by Broca (1865), Dronkers (1996), and Hillis et al. (2004), the current study sought to examine the relationship between impaired speech production and cortical structure and function in chronic stroke patients in a voxel-wise analysis. Advancements in neuroimaging and analysis techniques have enabled the use of more precise and sensitive methods than those employed previously. Lesions were demarcated on native high-resolution pathological images before normalization, resulting in precise lesion maps. We then utilized high-resolution MRI to examine the relationships between frank structural damage and AOS. We used whole-brain MRI assessments of cerebral blood flow (CBF), acquired with pulsed arterial spin labeling (PASL), in order to examine the relationship between AOS and possible brain dysfunction in structurally intact tissue.

2. Results

Lesion and CBF overlap maps for the entire patient group are illustrated in Figure 1. Lesion overlap analysis, illustrated in Figure 2, revealed the maximal lesion overlap for patients with AOS (26/26) in left middle insula (MNI=-36,-14,16); patients without AOS (12/24) demonstrated greatest lesion overlap in left posterior middle temporal lobe (MNI=-50,-44,10). Binary and continuous whole-brain voxel-wise analyses revealed a robust relationship between AOS and structural brain damage mostly involving LIPCpo, $Z=3.66$, $p<.01$, and $Z=3.44$, $p<.01$, respectively. A much smaller number of significant voxels were found in the insula in both analyses (Figure 3). The whole brain CBF analysis did not yield statistically significant results.

A step-wise regression analysis examining proportional damage in LIPCpo, LIPCpt, LAIns, and LPIIns yielded one significant model: increased damage to LIPCpo alone was the strongest predictor of AOS (binary), $F(1,48)=79.802$, $p<.0001$, $R^2=.62$ and AOS (continuous), $F(1,48)=191.417$, $p<.0001$, $R^2=.80$. Additionally, the full model (all VOI's) yielded statistically significant prediction of AOS (binary), $F(4,45)=22.094$, $p<.0001$, $R^2=.663$, and AOS (continuous), $F(4,45)=51.638$, $p<.0001$, $R^2=.821$. Stepwise regression of CBF values in the four VOI's yielded one significant model: decreased CBF in LIPCpo alone predicted AOS (binary), $F(1,41)=15.431$, $p<.0001$, $R^2=.273$, and AOS (continuous), $F(1,41)=19.866$, $p<.0001$, $R^2=.326$. The full model was statistically significant as well for AOS (binary), $F(4,38)=3.795$, $p=.01$, $R^2=.285$, and AOS (continuous), $F(4,38)=4.965$, $p=.003$, $R^2=.343$. All VOI's examined were significantly correlated with AOS (binary and continuous), both for proportional damage, $r(48)$ range = .596 to .894, all $p<.0005$, and for CBF, $r(41)$ range=-.441 to -.571, all $p<.003$; LIPCpo represented the maximum correlation

in each case. All VOI's were also significantly correlated with each other, again for both factors: proportional damage $r(48)$ range =0.586 to 0.883, all $p<.0005$; CBF $r(41)$ range=0.662 to 0.91, all $p<.0005$.

3. Discussion

At first glance, lesion overlap analysis and voxel-wise lesion analysis appear to provide conflicting results in this study. The lesion overlap analysis highlights the insula as consistently damaged in patients with AOS, supporting previous research (Dronkers, 1996; Ogar et al., 2006) that found LAIns damage was the most robust predictor of speech impairment in post-stroke patients, most with concomitant aphasia. Unlike Dronkers and colleagues, we did not see a complete sparing of the LAIns in patients without AOS; at least 9 patients without AOS had LAIns damage. Additionally, it can be observed from the overlap maps that patients without AOS did not generally have damage to Broca's area, highlighting the importance of this area for intact motor speech abilities. Therefore, both the overlap and the voxel-wise analyses are consistent with Broca's initial findings, revealing that impaired speech articulation, specifically AOS, is most reliably associated with damage to Broca's area. As importantly, we found that Broca's area involvement is a better predictor of AOS than damage to the insula. Our findings are accordant with Hillis and colleagues (2004) who found that Broca's area damage is a more reliable predictor of motor speech impairment compared to left insula involvement.

It is noteworthy that the cluster wherein damage predicted AOS was mostly located in the LIPCpo with far less inclusion of the LIPCpt (Figure 3). Although Broca's area is commonly referred to as a single region, its different sub-regions probably vary substantially with regard to their specific roles in speech and language (Amunts et al., 1999). The caudal portion of Broca's area - *pars opercularis* (LIPCpo), roughly corresponding to Brodmann's area (BA) 44 - has been suggested to play a crucial role in motor speech programming (Bohland and Guenther, 2006; Guenther, 2006; Guenther et al., 2006) whereas *pars triangularis* (LIPCpt), BA 45, perhaps plays a greater role in language specific programming (Newman et al., 2003; Rodd et al., 2010). Our data cannot elucidate the specific role of LIPCpo in speech production, whether it is responsible for planning of motor speech movements or, for example, storage of specific motor speech maps that are selectively activated for speech production.

The current results suggest that damage to the posterior portion of Broca's area is a better predictor of AOS than insula involvement; yet, they do not discount the role of the LAIns in speech processing. Although the insula has been implicated in a variety of clinical sequela, studies involving humans as well as non-human primates commonly emphasize the visceral role of this region (Augustine, 1996). In 2004, Ackerman and Riecker reviewed previous work in which insula activation was only noted in overt, and not covert, speech production, leading authors to argue against the traditional motor planning role assigned to the insula; they asserted that the insula is actually involved in the selection and coordination of muscles involved in speech. This is supported by observations of significant bilateral anterior insula activation during overt syllable production (GO) trials, regardless of sequence or syllable complexity, but not for NOGO trials during which the participants prepared for syllable

production (Bohland & Guenther, 2006). These and other findings led Ackermann and Riecker (2010a) to suggest that the insula may play a role in modifying respiration for speech production rather than having a specific role in motor planning of the articulators. In this context, the current findings emphasize the importance of LIPCpo in speech articulation whereas the insula, perhaps both left and right, may play an important role in modifying an autonomic function (i.e., respiration) during speech production.

As several reports have stressed, lesion distribution in stroke is constrained by the distribution of the three major vascular branches (Cheng et al., 2011; Lee et al., 2004; Rovira et al., 2005; Tatu et al., 1998). Equally important, stroke-related damage to one cortical region is also predictive of damage to other regions within the same vascular distribution. Consequently, using lesion analyses to determine the specific function of adjacent regions may be limited if both are irrigated by the same cerebral artery. One way to ameliorate this limitation is to employ a VOI analysis and compare the relative association of each region with the dependent factor, which, in this case, was AOS. In the current study, we examined several regions implicated in impaired speech articulation (LIPCpo, LIPCpt, LAIns and LPIns), and found that though each was highly correlated with AOS both for structural damage and decreased CBF, LIPCpo was the dominant statistical predictor of deficit, a pattern also well illustrated in our voxel-wise analysis. It is also worth noting here that the voxel cluster associated with AOS was not entirely confined to LIPCpo but also involved the precentral gyrus (Figure 3), an area that others have implicated in motor speech (e.g., Ackermann & Riecker, 2010b; Square-Storer et al., 1997).

Because adjacent regions are very often engaged in the same or related behaviors, vasculature also drives a strong correlation of symptoms observed in patients, with some clusters or combinations of symptoms and disorders more common than others. Likewise, functional disruption of one node in a network may lead to disruption in other nodes. This limits the ability of statistical methods to disentangle the functional modules involved. For example, AOS is most often concomitantly observed with language deficits such as anomia, agraphia, agrammatism, etc. While previous studies (as well as our current approach) investigate these symptoms in isolation, there is a clear need for future studies to understand the relationship between these symptoms. One solution would be to acquire data from a very large sample of patients. Alternatively, techniques such as brain stimulation (where the location of brain disruption is chosen by the investigator and independent of vasculature) could be used to tease apart these different symptoms.

Our findings in chronic patients are in agreement with research in acute patients (Hillis et al., 2004), yet it is clear that we are in conflict with two studies by Dronkers who also examined AOS in chronic stroke patients (e.g., Dronkers, 1996; Ogar et al., 2006). We speculate that the discrepancy in findings may reflect the improved sensitivity of our analysis methods. For example, we drew lesions on native high-resolution pathological scans, eliminating the need to re-create the lesion on a standard template and extrapolate lesion boundaries that cannot be visualized on clinical scans with large gaps between slices (Rorden & Brett, 2000). High-resolution anatomical images and cost-function lesion masking were then used for precise normalization. Voxel-wise lesion symptom mapping analysis was employed (with lesion size included as a covariate), which has proven to be a

methodological improvement relative to lesion overlap analysis when exploring brain-behavior relationships (Rorden & Karnath, 2004).

Although Broca's description of Leborgne's brain damage clearly included other regions such as left inferior parietal lobe and insula, our results support that he was, indeed, correct in attributing acquired motor speech impairment to involvement of LIPC. Crucially, our analyses may explain contradictory findings, in that even though Broca's area damage most strongly predicts AOS, other regions, particularly those with shared vasculature, (e.g., insula), are often affected in stroke.

4. Materials and Methods

4.1 Patients

Fifty patients (25 females) with chronic stroke and concomitant aphasia were included in this study. The mean patient age was 60 years ($SD=12$). All had incurred a single event stroke to the left hemisphere at least 4 months before study inclusion ($M=47$ months, range =4-350). All patients were evaluated with a battery of neuropsychological tests, including the Western Aphasia Battery (WAB; Kertesz, 1982), and were assigned an aphasia quotient (AQ), which is a measure of aphasia severity that ranges from 0 to 100. The mean AQ for the group was 57.89 ($SD=27.35$; range=5.7-95). Patients were also given the Apraxia Battery for Adults – Second Edition (ABA-2; Dabul, 2000), which requires patients to complete diadochokinetic, repetition, and naming tasks.

4.2 AOS rating

To assess AOS, two experienced (10+ years each) speech-language pathologists (SLP's) determined the presence and severity of AOS on a scale of 0 to 7 (where 0 indicates AOS is absent and 7 indicates severe AOS) following extensive clinical interaction (assessment and/or treatment) and video review of WAB and ABA-2 administration. Patients receiving a score greater than 0 were considered to have AOS for the binary classification, and must have demonstrated the following characteristics that could not be attributed to aphasia or dysarthria: 1) effortful, trial-and-error, groping articulatory movements and attempts at self-correction, 2) dysprosody unrelieved by extended periods of normal rhythm, stress, and intonation, and 3) obvious difficulty initiating utterances (adapted from Wertz et al., 1984). Of 50 patients rated, 48 were assigned the same AOS classification (present or absent; 96% agreement) by the two SLPs; the remaining two patients were classified following a common review of each case. Continuous severity ratings provided by the two SLPs were averaged; ratings were highly correlated, $r(48)=.953$, $p<.0001$. Twenty-six patients had AOS while 24 did not. The mean severity rating for patients with AOS was 5.57; the mean AQ for patients with AOS was 46.25 ($SD=23.58$) with the following aphasia subtypes represented: 5 anomic, 15 Broca's, 1 conduction, 3 global, 1 transcortical motor, 1 unclassified. Mean patient age and months post onset (MPO) for this subgroup was 56 years ($SD=12$) and 66 MPO ($SD=84$). The mean AQ for patients without AOS was 71.04 ($SD=25.68$) with the following aphasia subtypes represented: 15 anomic, 1 Broca's, 4 conduction, and 4 Wernicke's. Mean patient age and MPO for this subgroup was 65 years ($SD=12$) and 26

MPO ($SD=20$). The study was approved by the University of South Carolina's Institutional Review Board and informed consent was obtained from all patients.

4.3 Neuroimaging

MRI data were collected using a 3T Trio system (Siemens Medical, Erlangen, Germany) with a 12-element head coil. All patients were scanned with high-resolution T2 and T1 MRI sequences. The T2 sequence utilized a SPACE (Sampling Perfection with Application optimized Contrasts by using different flip angle Evolutions) protocol with the following parameters: field of view (FOV) = 256×256 mm, 160 sagittal slices, variable degree flip angle, TR = 3200 ms, TE = 352 ms. The T1 sequence utilized a turbo field echo sequence (MP-RAGE) with the following parameters: FOV = 256×256 mm, 160 sagittal slices, 15 degree flip angle, TI=900ms, TR = 9.5 ms, TE = 5.7 ms. Lesions were demarcated on axial slices of native T2-MRI images using MRICron. Structural images were prepared for data analysis using software designed and supported by the Oxford Centre for Functional MRI of the Brain (FMRIB) - FMRIB's Software Library (FSL) version 4.1 (Smith et al., 2004). Native cropped and skull-stripped structural MRI images were coregistered and then normalized to the standard MNI 152 template, employing lesion mask weighting for improved accuracy. The transformation matrix for normalization was applied to the lesion. Normalized images were resliced to 2 mm isotropic.

Two Pulsed Arterial Spin Labeling (PASL) sequences were used to acquire cerebral blood flow measures. Twenty patients were scanned with the following parameters: parallel imaging GRAPPA factor = 2, $3.5 \times 3.5 \times 6$ mm voxels, 16 axial slices, TR = 4000 ms, TE = 12 ms. Twenty-three patients were scanned with the following parameters: parallel imaging GRAPPA factor = 2, $3 \times 3 \times 6$ mm voxels, 14 axial slices, TR = 2500 ms, TE = 11 ms. For both sets of patients, estimates of equilibrium magnetization (M_0) were obtained. Images were corrected for head motion. Each patient's perfusion images were coregistered to their own spatially normalized structural images. To address cross-subject variations in global CBF, the intensity of the perfusion data was normalized. Specifically, we separately calculated the mean intensity in the right (unaffected) hemisphere for the gray and white matter. These two values were used to calculate a slope and intercept such that the white matter had a mean intensity of 1.0 and the gray matter had a mean intensity of 2.0. All voxels throughout the brain were scaled and translated based on these values. Note that out of the 50 patients included in this study, only 43 underwent PASL.

4.4 Data analysis

For comparison with previous studies, overlap of normalized lesions for patients with and without AOS was examined. For more accurate identification of the critical lesion location associated with AOS, we performed voxel-wise lesion-symptom mapping (VLSM) using Non-Parametric Mapping (NPM), implemented in MRICron (Rorden, Karnath, & Bonilha, 2007). For all VLSM analyses, permutation thresholding ($n=1000$) was applied in order to control family wise error rate. Lesions were quantified as binary lesion maps (lesion vs. no lesion). To facilitate comparison with previous studies, a qualitative (i.e., presence versus absence of AOS treated as a binary classification) VLSM analysis was performed on a voxel-by-voxel basis. In a complementary quantitative VLSM analysis, damage among

patients was examined with AOS severity entered as a continuous factor (based on the SLPs ratings of AOS). For both analyses, lesion size was included as a covariate to minimize the influence of the extent of damage in predicting AOS. Specifically, statistics were computed using logistic regression, which allows the inclusion of lesion volume as a nuisance regressor (Karnath et al., 2004).

To examine the association between localized CBF and AOS, t-tests were run for each voxel where the level of CBF was compared between patients with and without AOS (binary) and according to AOS severity (continuous). For these analyses, the statistics for each voxel were restricted to individuals where this voxel is intact (i.e., not part of the lesion).

A priori volume of interest (VOI) analyses were performed in SPSS 19.0 (SPSS, Inc.), using both stepwise (p -enter=0.05, p -remove=0.10) regression and the full model, to determine how AOS (binary and continuous) was influenced by proportional damage and mean CBF in four left hemisphere regions: LIPCpo, LIPCpt, LAIns, and LPIns. VOIs were derived from the automated anatomical labeling (AAL) maps as implemented in the Wake Forest Pickatlas (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002), with the insula being subdivided along the anterior-posterior plane in reference to its center of mass.

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Apraxia of speech is most reliably associated with Broca's area damage.
The left pars opercularis was the strongest predictor of apraxia of speech.
Perfusion deficits in the left pars opercularis predicted apraxia of speech.
Broca's area damage is a better predictor of apraxia of speech than insula damage.

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Figure 1.

A lesion overlay map (top panel) showing the distribution of brain damage for the patient group (N=50). The color scale indicates the proportion of lesion overlap, from blue (least overlap) to red (most overlap, where at least 33 patients had damage). A perfusion overlay map (bottom panel) showing average perfusion for the patient group (N=43). Values shown are relative to CBF values (gray and white matter) in the non-affected right hemisphere, from blue (areas of relatively lower LH perfusion) to red (areas showing less overall difference between the hemispheres).

Figure 2.

A lesion overlay map (top panel) illustrating left hemisphere lesion distribution among patients with AOS (N=26). The greatest lesion overlap was found in the left middle insula (N=26/26; $-36, -14, 16$). Average lesion size for the AOS group was 181.05 cc ($SD=104.29$, range=27.38–420.45). The bottom panel is the lesion overlay map illustrating left hemisphere lesion distribution among patients without AOS (N=24). The greatest lesion overlap was found in the left superior temporal lobe (N=12/24; $-50, -44, 10$). Average lesion size for the group without AOS was 71.46 cc ($SD=80.34$, range=6.27–274.36).

Figure 3.

Whole brain voxel-wise analyses, with AOS severity entered as a continuous factor, revealing structural damage associated with apraxia of speech. Green and blue areas highlight Broca's area (LIPCpo and LIPCpt) and insular areas (LAIns and LPIIns), respectively; these VOIs were derived from the automated anatomical labeling (AAL) maps. The color scales show the magnitude of the statistical relationship between location of structural damage in relation to AOS. The yellow color scale illustrates the significant cluster overlapping with Broca's area; the red color scale illustrates the significant cluster that does not overlap with VOIs selected *a priori*. Within each VOI, the proportion of voxels overlapped by the significant cluster (continuous) is as follows: LIPCpo = .824; LIPCpt = .247; LAIns = .147; LPIIns = .175.