Brain & Language 123 (2012) 125–130

Contents lists available at SciVerse ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Short Communication

Re-establishing Broca's initial findings

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ARTICLE INFO

Article history:
Accepted 28 August 2012
Available online 8 October 2012

Keywords:
Aphasia
Apraxia
Cerebral blood flow
Broca
Insula
Lesion
MRI
PASL
Perfusion
Pre-frontal cortex

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.

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 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, 2013). 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 (Auburtin, 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, 2013).

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

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http://dx.doi.org/10.1016/j.bandl.2012.08.007

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 et al. (2004) 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 Fig. 1. Lesion overlap analysis, illustrated in Fig. 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, $Z = 3.66$, $p < 0.01$, and $Z = 3.44$, $p < 0.01$, respectively. A much smaller number of significant voxels was found in the insula in both analyses (Fig. 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 LPIns yielded one significant model: increased damage to LIPCpo alone was the strongest predictor of AOS (binary), $F(1,48) = 79.802$, $p < 0.0001$, $R^2 = 0.62$ and AOS (continuous), $F(1,48) = 191.417$, $p < 0.0001$, $R^2 = 0.80$. Additionally, the full model (all VOI's) yielded statistically significant prediction of AOS (binary), $F(4,45) = 22.094$, $p < 0.0001$, $R^2 = 0.663$, and AOS (continuous), $F(4,45) = 51.638$, $p < 0.0001$, $R^2 = 0.821$. Stepwise regression of CBF values in the four VOI's yielded one significant model: decreased CBF in LIPCpo alone predicted AOS (binary), $F(1,41) = 15.431$, $p < 0.0001$, $R^2 = 0.273$, and AOS (continuous), $F(1,41) = 19.866$, $p < 0.0001$, $R^2 = 0.326$. The full model was statistically significant as well for AOS (binary), $F(4,38) = 3.795$, $p = 0.01$, $R^2 = 0.285$, and AOS (continuous), $F(4,38) = 4.965$, $p = 0.003$, $R^2 = 0.343$. All VOI's examined were significantly correlated with AOS (binary and continuous), both for proportional damage, $r(48)$ range = 0.596–0.894, all $p < 0.0005$, and for CBF, $r(41)$ range = −0.441 to −0.571, all $p < 0.003$; 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 = 0.586–0.883, all $p < 0.0005$; CBF $r(41)$ range = 0.662–0.91, all $p < 0.0005$.

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 et al. (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 (Fig. 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 & Guenther, 2006; Guenther, 2006; Guenther, Ghosh, & Tourville, 2006) whereas *pars triangularis* (LIPCpt), BA 45, perhaps plays a greater role in language specific programming (Newman, Just, Keller, Roth, & Carpenter, 2003; Rodd, Longe, Randall, & Tyler, 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 Ackermann and Riecker (2004) , 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