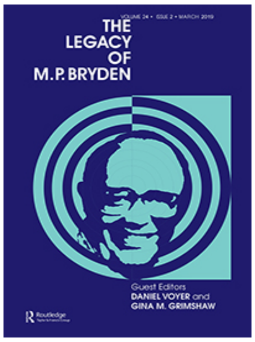

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Fundamental or forgotten? Is Pierre Paul Broca still relevant in modern neuroscience?

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ABSTRACT
The ability to speak is a unique human capacity, but where is it located in our brains? This question is closely connected to the pioneering work of Pierre Paul Broca in the 1860s. Based on post-mortem observations of aphasic patients' brains, Broca located language production in the 3rd convolution of the left frontal lobe and thus reinitiated the localizationist view of brain functions. However, contemporary neuroscience has partially rejected this view in favor of a network-based perspective. This leads to the question, whether Broca's findings are still relevant today. In this mini-review, we discuss current and historical implications of Broca's work by focusing on his original contribution and contrasting it with contemporary knowledge. Borrowing from Broca's famous quote, our review shows that humans indeed "speak with the left hemisphere"– but Broca's area is not the sole "seat of articulatory language".

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KEYWORDS Pierre Paul Broca; aphasia; Broca's area; speech production; functional neuroanatomy; language lateralization

Comment

"Nous parlons avec l'hémisphère gauche"
(We speak using the left hemisphere)

Pierre Paul Broca, 1865

Every psychology and medical student learns about Broca's area, a brain region named after famous French neurologist Pierre Paul Broca. This year marks the 150th anniversary of his influential speech in Norwich, England, when he proclaimed that the seat of articulatory language is localized to

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the 3rd convolution of the left frontal lobe (Lorch, 2008). In the 1860s, the idea that cognitive functions may be localized to specific brain regions was seen as an offshoot of phrenology by many of Broca's contemporaries, and localization theories were mostly criticized. However, Broca's hypothesis on the seat of articulatory language was well supported by evidence and represents a major milestone in the history of functional neurology. Modern neuroscience, however, has shifted from a localizationist view of brain function to a network-based perspective. And with this shift in perspective, some might argue that ideas and concepts of the past are as dead as their advocates (Tremblay & Dick, 2016). This brings us to one question: Are Broca's findings still relevant in modern neuroscience?

In late 2017, we, a group of young neuroscientists, visited Paris to follow the path that Paul Broca walked 150 years prior: from examining the very brains on which Broca based his theories, to visiting the lecture theatre of the society of Anthropology that Broca helped found, to paying our respects at the site where he was buried. What impact does Broca have on us as modern scientists beyond his obvious role in the history of our discipline?

To answer this question, we report on several current and historical implications of Broca's work, by focusing on his original contribution and contrasting it with contemporary knowledge. First, we discuss Broca's neuroanatomical observations of the lesions that give rise to Broca's aphasia. Second, we review his proposal that the left frontal cortex is the "seat of articulatory language". Finally, we turn our attention to Broca's claims of left hemispheric superiority in speech production more broadly.

The neuroanatomical substrates of Broca's aphasia

Broca's theory was built on his studies of aphasic patients, who showed severe language impairments. Importantly, post-mortem examinations revealed that the vast majority of these patients had tissue damage to approximately the same brain region – suggesting that functional localizations in the brain do exist. Of the 18 brains that Broca collected before formally articulating his theory on language localization, those of his first two aphasic patients, Messieurs Leborgne and Lelong, are still preserved by the *Jussieu Campus* of the *Université Pierre et Marie Curie* in Paris.

Bundled up against the chilly autumn wind, we made our way through the maze of corridors and staircases of the Jussieu campus until we were brought to an inconspicuous metal door that led to the University's basement. Here, preserved animal and human specimens that were once used to study pathology and anatomical malformations caused by disease (predominantly syphilis and tuberculosis) sit like trophies of a time gone by. Safely kept on a shelf at the back of the room, Leborgne's brain is placed at eye level so that the most significant area of damage is easily visible (Figure 1).

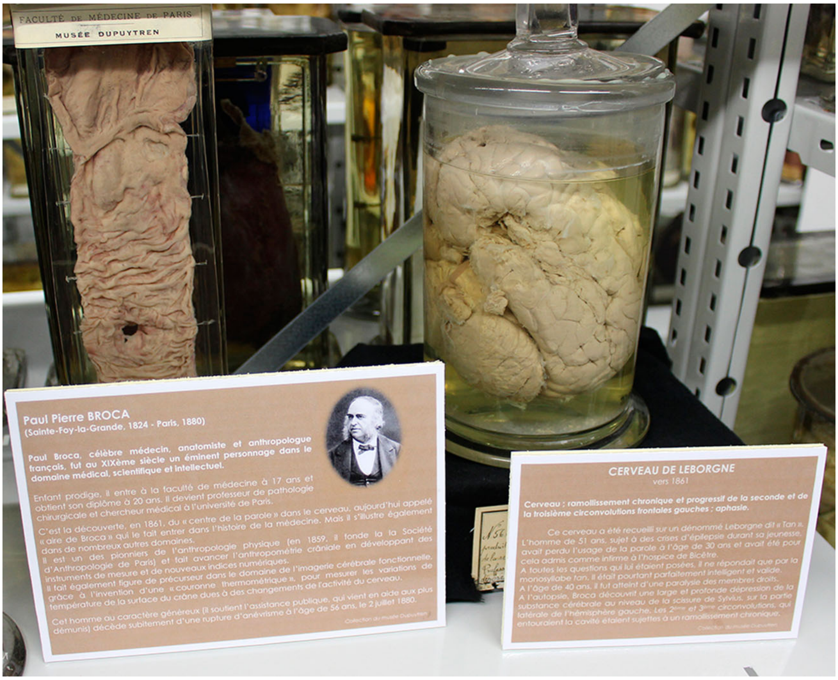

Figure 1. The brain of Monsieur Leborgne. The specimen on the right is the preserved brain of Monsieur Leborgne, who Broca met in April 1861 (Leblanc, 2017). The damage in the frontal lobe is evident and takes the shape of a focal lesion. This image was taken with permission from the *Université Pierre et Marie Curie*.

On the same set of shelving, one down from Leborgne's brain, lays the specimen of Lelong's brain, from whom only the left hemisphere is preserved (Figure 2). Seeing these two famous brains in person is awe-inspiring, but also somewhat sobering. It is strange to see such celebrated pieces of neuroscientific history to be exactly this: a brain on a shelf. It was with these two patients that Broca coined the term "aphemia" (now known as "aphasia"): an impairment of speech production that does not affect intelligence. We find ourselves wondering once more: is Pierre Paul Broca's theory simply a relic of the past?

Today, the term "Broca's aphasia" formally refers to impairment in verbal expression, which includes both apraxia of speech and agrammatism (Benson & Ardila, 1996; Berndt & Caramazza, 1980; Goodglass, 1999). In addition, Broca's aphasic patients show comprehension deficits on the lexical, morphological, and sentence level (Dick & Bates, 2000; Grodzinsky, Pinango, Zurif, & Drai, 1999). The advent of neuroimaging brings contradicting evidence to the classical view that Broca's aphasia is based on damage to Broca's area (Ardila, Bernal, & Rosselli, 2016), because it also requires damage to adjacent cortical regions and white matter, including the insula, inferior parts of the motor cortex, the basal ganglia, and subcortical and

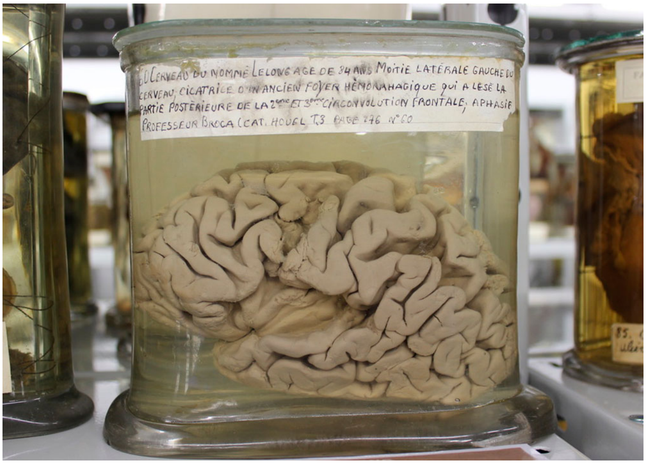

Figure 2. The brain of Monsieur Lelong. Broca encountered Lelong in October, 1861. After suffering a stroke in 1860, Lelong's vocabulary was reduced to a handful of words. An autopsy by Broca revealed a focal lesion in approximately the same area as in Leborgne's case (Leblanc, 2017). This image was taken with permission from the *Université Pierre et Marie Curie*. Translation: The brain of Lelong, aged 34. The left lateral portion of the brain with a scar caused by an old hemorrhage, which lesioned the posterior part of the 2nd and 3rd frontal convolution; aphasia. Professor Broca. Translation (left plaque): Paul Pierre Broca (Sainte-Foy-la-Grande, 1824 – Paris, 1880): Paul Broca, famous physician, anatomist, and French anthropologist, was an outstanding personage in the medical, scientific and intellectual domains. A child prodigy, he started at the Faculty of Medicine at 17 years old, and received his diploma at the age of 20. He became a surgical pathology professor and medical researcher at the University of Paris. He rose to fame in 1861 with his discovery of the "seat of articulatory language" in the brain, known today as "Broca's area". However, he also became renowned in many other domains. He was one of the pioneers of physical anthropology (in 1859, he founded the Parisian Society of Anthropology) and helped advance the study of cranial anthropometry through his development of instruments to measure new numerical indices. He was also a precursor in the development of functional brain imaging due to his invention of the "thermometric crown", which measures variations in skull temperature caused by brain activity. This generous man (a supporter of public assistance which aided the destitute) passed away suddenly from an aneurysm at the age of 56 on the 2 July 1880. Translation (right plaque): The Brain of Leborgne (ca. 1861): Chronic and progressive softening of the second and third left frontal convolutions: aphasia. This brain is from a man named Leborgne, also known as "Tan". The 51 year old man, who suffered from epilepsy during his youth, lost the ability to speak at the age of 30 and was admitted to the Bicètre Hospital. When asked questions, he could only respond with the single syllable *tan*, despite being perfectly intelligent and able to comprehend what was being asked. At 40, he experienced paralysis in his right limbs. During autopsy, Broca discovered a very large depression in the brain at the level of the Sylvian fissure, on the lateral part of the left hemisphere. The second and third convolutions, which surrounded this cavity, suffered from chronic softening.

periventricular white matter (Benson & Ardila, 1996; Mohr et al., 1978). Moreover, a report by Fridriksson, Bonilha, and Rorden (2007) describes a patient who suffered from Broca's aphasia despite having no damage at all to Broca's area. One explanation of this so-called "sub-cortical Broca's aphasia" is that damage to the left subcortical striatocapsular region leads to decreased cerebral bloodflow in nearby cortical areas. Therefore, the overlying Broca's area suffers from hypoperfusion (Choi et al., 2007). However, in the study of Fridriksson and colleagues, Broca's area showed increased BOLD activity during an overt picture-naming task, thereby casting doubt on the hypoperfusion explanation. Besides, other studies also indicate that damage to the basal ganglia (Damasio, Damasio, Rizzo, Varney, & Gersh, 1982; Kang, Sohn, Han, & Paik, 2017) or thalamus (Maeshima et al., 2011) can lead to similar aphasic syndromes.

Further contradiction of the unique role of Broca's area in Broca's aphasia comes from an MRI study on Leborgne's and Lelong's brains themselves (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007). Dronkers and colleagues re-evaluated the extent and sites of the lesions, finding that damage in both patients exceeds the posterior part of the third frontal convolution. Moreover, both patients display additional unique sites of damage. In Leborgne's case, this includes subcortical structures, the insula, and white matter bundles such as the superior longitudinal fasciculus and frontal-parietal periventricular white matter. Importantly though, all tissue damage was found in the left hemisphere while the right hemisphere was spared. In the case of Lelong, from whom only the left hemisphere is preserved, MRI revealed previously unreported damage, including small lesions in the superior longitudinal fasciculus and severe atrophy in the insula. Furthermore, the frontal lesion that was originally described by Broca only covers the pars opercularis, which hosts Brodmanns area 44. In contrast, the pars triangularis (approximately representing Brodmanns area 45) was spared. Given that the typical anatomical definition of Broca's area includes both the pars opercularis and pars triangularis (Tremblay & Dick, 2016), this suggests, in line with current thinking, possible functional segregation within Broca's area. Taken together, Broca's conclusion on the neural substrate of aphasia seems partly right, but damage to Broca's area is neither necessary nor sufficient to produce Broca's aphasia.

The "seat of articulatory language" and its function

Based on his clinical observations, Broca proclaimed that the third frontal convolution of the left hemisphere is the seat of articulatory language (Broca, 1865) – a claim which echoes the rather outdated assumption that a particular brain region governs a particular cognitive ability. In fact, imaging studies suggest that Broca's area is associated with numerous diverse aspects of language production, such as the acquisition of language syntax (Tettamanti et al., 2002), and representation of sound during and before language generation (Magrassi, Aromataris, Cabrini, Annovazzi-Lodi, & Moro, 2015). Moreover, Moro et al. (2001) showed PET activation in Broca's area in both morphological and syntactic processing. However, the pattern of co-activated regions differed between syntactic and phonotactic processing. Although details vary according to specific models, current frameworks of language processing thus emphasize that speech is dependent on the dynamic interaction of several brain regions (Friederici, 2011; Hickok & Poeppel, 2007; Tourville & Guenther, 2011). Nevertheless, Broca's finding on the importance of "his area" in language production prevails, given that all contemporary language theories ascribe a key role to the left inferior frontal gyrus. An example can be found in the MUC (memory, unification, control) framework of Peter Hagoort. In his theory, Hagoort argues that Broca's area is crucial for the unification of word information into larger units on the phonological, syntactic, and semantic level (Hagoort, 2005). In line with this proposal, Flinker et al. (2015) suggest that during word production, the neural representation of a word is forwarded from posterior sensory areas to anterior motor areas of the left hemisphere. In their study, Broca's area was involved in co-ordinating the transformation of a word's neural representation to an articulatory code, which in turn is implemented by motor cortices that co-ordinate articulation.

While there is considerable effort to clarify the specific role of Broca's area in language processes, it is now thought to also contribute to various non-linguistic cognitive functions. The general tenet of current neuropsychological thinking is that brain regions are likely to participate in more than one network. In line with this, Broca's area has been found to participate in diverse cognitive processes, including action recognition (Hamzei et al., 2003), movement preparation (Thoenissen, Zilles, & Toni, 2002), and sentence comprehension (Kuhnke, Meyer, Friederici, & Hartwigsen, 2017); but also in the execution and perception of music (Fadiga, Craighero, & D'Ausilio, 2009). The observation that Broca's area is involved in many different cognitive processes raises debate between language-specific and domain-general views of Broca's area. Importantly, both sides might be right, because two sets of functional sub-regions within Broca's area can be identified, spanning over the anatomical boundaries of the pars opercularis and pars triangularis: one central part involved in language-specific processes, which is surrounded by another functional part that engages in multiple task domains (Fedorenko, Duncan, & Kanwisher, 2012) (Figure 3).

Cytoarchitectonically-defined subparts of Broca's area also show functional segregation. For example, BA45 is more involved in the production of "semantic" words relative to "overlearned" words than BA44 (Amunts et al., 2004). In contrast, BA44 is thought to be more involved in phonological processes, given that BOLD activation levels are higher in phonological fluency tasks

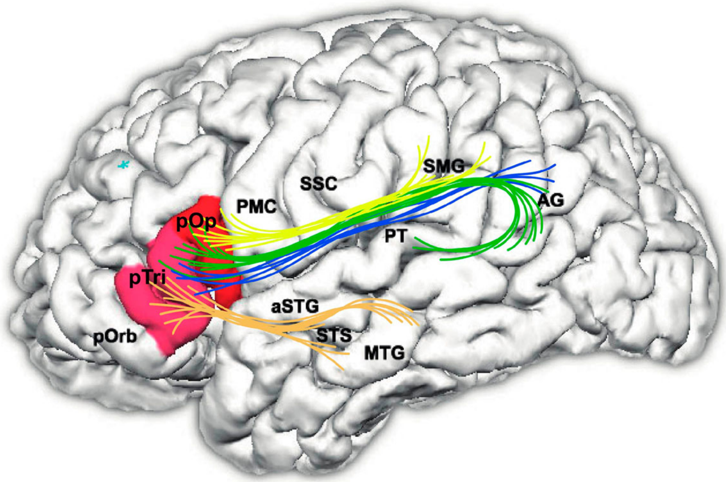

Figure 3. White matter pathways from Broca's area to other language-related regions. Coloured regions indicate Broca's area subparts (pOp = pars opercularis; pTri = pars triangularis). Coloured lines indicate parts of different white matter bundles (please see online version for explanation: green = arcuate fasciculus; ocher = extreme capsule fasciculus; yellow = third branch of superior longitudinal fasciculus; blue = second branch of superior longitudinal fasciculus). The remaining labels indicate different brain regions (pOrb = pars orbitalis; PMC = primary motor cortex; SSC = somatosensory cortex; SMG = supramarginal gyrus; AG = angular gyrus; aSTG = anterior part of superior temporal gyrus; STS = superior temporal sulcus; MTG = medial temporal gyrus; PT = planum temporale). Adapted after Petrides (2014).

compared to semantic or verbal fluency tasks (Heim, Eickhoff, & Amunts, 2008). Keeping this functional differentiation in mind, it is unsurprising that the two constituting parts of Broca's area differ in their cyto- and receptor architectonic structure (Amunts et al., 2010), as well as in their structural (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Frey, Campbell, Pike, & Petrides, 2008) and functional connectivity patterns (Jakobsen et al., 2016; Margulies & Petrides, 2013). Therefore, Broca's area is now understood as a heterogeneous but still central part of the language network, and less as a homogeneous brain region that hosts the faculty of speech articulation (Figure 3).

Lateralization of speech production

Pierre Paul Broca died on 9 July 1880. His remains were buried in the Montparnasse Cemetery in Paris where his family tomb still stands today (Figure 4). Broca's ideas, however, live on together with the preserved brain specimens of Leborgne and Lelong. When Broca originally examined these brains in

Figure 4. The tomb of the Broca Family in the Montparnasse Cemetery, Paris.

1861, he refused to reject Bouillaud's theory that both hemispheres were involved in articulatory language (Leblanc, 2017). It would take him four more years and sixteen more cases before he argued in favour of the left hemisphere in his fundamental publication entitled "On the Seat of Articulatory Language" (1865).

This final insight of Broca's work prevails in contemporary research in that the dominance of the left hemisphere in articulatory language processes is generally accepted (Ocklenburg & Güntürkün, 2018). However, when dividing the language domain into its sub-processes, such as language comprehension and production, the picture becomes less clear. For example, the dual route model (Hickok & Poeppel, 2007) suggests the existence of two processing routes for speech: the dorsal stream, which supports the translation of auditory speech signals into articulatory representations; and the ventral stream, which is involved in speech comprehension. The ventral stream depends on spectro-temporal and phonological networks that are present in the superior temporal sulcus and gyrus of both hemispheres, thus implying bilateral processing. However, the dorsal stream, which contains Broca's area, is strongly left-lateralized (Hickok & Poeppel, 2007).

Similarly, the asymmetric involvement of the inferior frontal gyrus in articulatory language is well established in the literature. For instance, the laterality index, calculated as the activation difference between Broca's area and its right hemispheric homologue, is often used to evaluate the asymmetric involvement of the inferior frontal gyrus in a task of interest. Typically, the laterality index shows higher involvement of Broca's area compared to its right hemispheric homologue during picture naming (Bowyer et al., 2005) or word generation (Hertz-Pannier et al., 1997). There is also stronger beta or gamma-band desynchronization of Broca's area during silent reading (Hirata et al., 2004). These neuroimaging findings are highly congruent with the results of the Wada test to determine the language-dominant hemisphere. Notably, fMRI and MEG techniques show considerable overlap in frontal areas of their respective activation maps during verb generation tasks, indicating that leftward activation asymmetry is independent from the measure used (Pang, Wang, Malone, Kadis, & Donner, 2011). Moreover, Broca's area is predominantly activated during covert word generation in both children and adults (Gaillard et al., 2000). Thus, leftward laterality indices of the inferior frontal gyrus are consistent in verbal fluency tasks after the age of 7 (Gaillard et al., 2003).

Based on clinical studies with patients who suffer from mental illness, the leftward activation asymmetry of the inferior frontal gyrus may demonstrate normative language lateralization. For instance, the inferior frontal gyri show asymmetric involvement during lexical discrimination in healthy individuals, but more symmetric activation patterns in patients suffering from schizophrenia or schizoaffective disorder (Li et al., 2007). Likewise, schizophrenic patients show a hemisphere-wide reduction in functional laterality during verb generation and semantic decision making (Sommer, Ramsey, & Kahn, 2001). Autism spectrum disorder is also associated with reduced leftward lateralization of the functional connectivity between Broca's area and speech perception regions, possibly reflecting a lack of hemispheric specialization (Nielsen et al., 2014).

Since Broca's initial findings were reported, many have assumed that Broca's area shows some form of structural asymmetry compared to its right hemispheric homologue (Keller, Crow, Foundas, Amunts, & Roberts, 2009), based on the idea that structural asymmetries between the left and right hemisphere lead to functional hemispheric asymmetries. However, studies on macrostructural left-right differences do not show definitive hemispheric asymmetries of the posterior inferior frontal gyrus (Herve, Crivello, Perchey, Mazoyer, & Tzourio-Mazoyer, 2006; Luders, Gaser, Jancke, & Schlaug, 2004; Ocklenburg, Friedrich, Güntürkün, & Genc, 2016b), thus indicating a dissociation between macroscopic asymmetry and language laterality. Given that functional hemispheric asymmetries might also result from the effect of intra- or interhemispheric white matter connectivity (Ocklenburg, Friedrich, Güntürkün, & Genc, 2016a), future studies might benefit from investigating the connectivity of Broca's area.

Conclusion

Broca's scientific contributions have had significant impact on modern research on functional brain localization and on the functional neuroanatomy of language. Thus, walking through the enchanting streets of Paris, where Broca himself once set foot 150 years ago, induces a sense of familiarity. Our scientific history is imbued in the very buildings of this city, pressed into these cobblestone alleyways by those who came before us, who thought before us.

Despite our respect for his legacy we need to acknowledge that many of Broca's ideas and conclusions have been proved wrong by his successors. Although there is little doubt about its importance in the neural language network, Broca's area is not the sole "seat of articulatory language", and its particular function in language is still a matter of debate. Furthermore, since Broca's area is implicated in a variety of other cognitive functions, the idea that it is exclusively a language area should be exchanged for a more domain-general view of brain structure and function. Modern neuroscientists should be cognizant of the functional and structural segregation within the posterior inferior frontal gyrus. Nevertheless, Broca's observation of left hemispheric dominance in language production still prevails in contemporary research, underlying the importance of functional hemispheric asymmetries. Borrowing from the famous quote of Paul Broca, we indeed speak with our left hemisphere – but it's a little more complicated than previously thought. In summary, Broca's legacy may no longer inform modern research on the neurobiology of language, but it has inspired us as young neuroscientists to dare question contemporary knowledge on the basis of carefully conducted experimental data. It is fitting, then, that these lauded brains still sit like hidden gems in the core of the city.

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