Broca’s region was originally described as a cortical site in the inferior frontal gyrus, where speech impairment occurs after brain lesions. However, this clinico-pathological definition does not define the underlying microstructural correlates. Two cytoarchitectonic areas (BA44, BA45) were identified as correlates of Broca’s region in the inferior frontal opercular and triangular parts, respectively. Recent microstructural analyses based on the distribution of transmitter receptors suggest a further segregation of BA44 and BA45 and the inclusion of neighboring areas in the adjacent inferior frontal and precentral sulci as well as in the frontal operculum as structural correlates of Broca’s region. Here, we review these recent cytoarchitectonic and receptorarchitectonic findings in Broca’s region, and compare them with functional imaging data containing sufficient topographical specifications. Finally, Broca’s region of the human brain is compared with the homologue region in the brain of apes, baboon and macaque monkey.

Introduction

Broca [1,2] identified a cortical lesion site in the left inferior frontal gyrus of a stroke patient who could only repetitively speak the syllable ‘Tan-tan’. Broca coined the term ‘aphemia’ for this functional deficit. The lesion site was later called Broca’s region. Observations in additional patients with similar or different speech disturbances and localizations of the lesion confirmed his initial reports [3]. Dronkers et al. [4] could study this historical brain. The images show that the lesion site did not only involve the gray matter of the posterior portion of the inferior frontal cortex, but also the underlying white matter as well as major parts of the basal ganglia and neighboring cortices. It became also clear, that the original concept of Broca’s region cannot elucidate the relationship between a lesion of well-defined cortical areas and specific speech deficits; for review of the Broca’s concept and its clinical-anatomical correlations (see Kellet et al. [5] and Tremblay and Dick [6*]). In addition to clinical data, neuroimaging studies in healthy subjects had to be used for understanding the functional segregation in Broca’s region by addressing more specific speech and language processes. The scope of the present review is to focus on recent cytoarchitectonic and receptorarchitectonic findings in Broca’s region, which reveal a previously underestimated degree of segregation, and to compare these findings with functional data.

The classical cytoarchitectonic concept of Broca’s region

Brodmann [7*] identified two cytoarchitectonic areas, BA44 and BA45, in Broca’s region, which occupied the opercular and triangular parts of the inferior frontal gyrus, respectively. The posterior border of BA 44 is at the level of the ventral part of the precentral sulcus. BA44 and BA45 are often, but not always, separated by the ascending ramus of the Sylvian fissure. Since this ramus and other sulci of Broca’s region are highly variable [8,9*], the border between both areas cannot reliably be defined based on sulcal patterns. Similarly, the horizontal branch of the lateral fissure does not provide a consistent landmark for the ventral border of BA45 [10,11]. Brodmann [7*] stated — without providing a detailed description — that BA47 of the orbital part of the inferior frontal gyrus shares various cytoarchitectonic features with BA44 and BA45, and thus summarized BA44, BA45 and BA47 under the term ‘subfrontal subregion’. Therefore, BA47 may be a candidate for inclusion in Broca’s region [12], which seems to be supported by its involvement in semantic encoding, attention to semantic relations, semantic relative to perceptual judgments, syntax, affective prosody, single word reading, and phonology [13–18]. However, we must keep in mind that Brodmann’s map represents a two-dimensional drawing of the surface of a brain, and did not provide any microstructural segregation within the deep sulci. Thus, the intra-sulcal surface may be occupied by previously undefined areas. Additionally, anatomical and neuroimaging...
Cytoarchitecture and myeloarchitecture of cortical areas in Broca’s region. (a) Cytoarchitecture of BA44. Note the clusters of very large pyramidal cells in layer IIIc (arrows). Modified after Amunts et al. [26].
(b) Cytoarchitecture of BA45. Note the clusters of very large pyramidal cells in layer IIIc (arrows). Modified after Amunts et al. [26].
(c) Most common myeloarchitectonic feature in Broca’s region. The myeloarchitectonic areas 56–59 and 53 are found within the extension of the myeloarchitectonic areas BA44, BA45 and BA47, and were myeloarchitectonically classified as unistriate or bistriate areas. In the unistriate areas, the outer and inner Baillarger stripes are not separate structures, but confluent and detectable as a single broad and myelinated stripe at the level of the myeloarchitectonic layers 4-5b. Delineations of the different areas within the unistriate cortex were recognized as variations of this basic type. The unistriate area 57 is comparable to the antero-dorsal part of BA44, whereas the unistriate areas 58–59 are comparable to BA45. (d) Myeloarchitecture of the bistriate area 56 (comparable to the posterior part of BA44) of Broca’s region. The bistriate regions of the isocortex are characterized by the outer and inner Baillarger stripes visible as separate structures at the level of the myeloarchitectonic layer 4 and 5b, respectively. Parts of the myeloarchitectonic area 53 may correspond to BA47. (e) Common myeloarchitectonic features of areas 39–43 on the precentral gyrus. These areas were myeloarchitectonically classified as parts of the unistriate region of isocortex, that is, only the outer Baillarger stripe is visible at the level of the myeloarchitectonic layer 4. All myeloarchitectonic Illustrations are modified after Vogt [27].

Present concepts of the microstructure of Broca’s region and its relationship to brain function

BA44 and BA45 are distinct from surrounding areas mainly by the presence of large pyramidal cells in deep layer III and in layer V (Figure 1). Furthermore, both areas show a lower cell packing density in layer VI. BA44 can be delineated from BA45 due to differences in layer IV: layer IV in BA44 is thin and invaded by pyramidal cells from neighboring layers III and V; that is, BA44 is ‘dysgranular’. Layer IV is clearly visible in BA45; that is, it is called ‘granular’ [26]. The dysgranular appearance of BA44 clearly separates it from granular cortical areas like BA45 and lateral prefrontal areas.

The classical cytoarchitectonic maps of Broca’s region [7,23] were supplemented in the first half of the last century by an increasing number of myeloarchitectonic studies. These studies provide evidence of a heterogeneity within BA47. A recent study employed resting-state functional connectivity and data-driven modularity optimization [19]. Previous cytoarchitectonic studies also resulted in a more complex segregation of this brain region [20–22].

von Economo and Koskinas [23] identified three cytoarchitectonic areas, which are completely or partly found on the frontal inferior gyrus. Their area FCBm corresponds to BA44, area FD1* to BA45, and area FF to BA47 [24]. The dysgranular area FCBm is located between the agranular premotor cortex and the granular prefrontal areas. It has large pyramidal cells in the deeper part of layer III (Figure 1), an inconspicuous layer IV (dysgranular isocortex), a layer V which can be further subdivided by a higher cell packing density in its upper than lower part, and a lacking sharp border between layer VI and the white matter. The cortical ribbon of FD1* is thinner than that of FCBm, but contains even larger pyramidal cells in deeper layer III (addressed by the Greek letter β in its name, which points to the size — ‘giganto’ meaning very large — of layer III pyramids; Figure 1), a distinct layer IV (granular isocortex), as well as prominent cell columns. In area FF, layers V and VI are wider than in FD1*, layer IV is thin, and all layers are less cell-dense than in FD [23]. Particularly, the part of BA47 which adjoins BA45 is a typical granular cortex with a well-developed layer IV, but moving to the orbital part of BA47 layer IV becomes less distinct. This suggests that BA 47 can be further segregated. Finally, BA47 largely differs from BA44 and BA45 by lacking very large pyramids in deeper layer III, and by its receptor fingerprint (see below). Semantic processing leads to activations in areas of the left ifs and in BA47 [25].
century by myeloarchitectonic observations, resulting in more fine-grained parcellations. Vogt [27] and Riegele [28] identified several areas in Broca’s region. This was confirmed in later observations [29–32]. The myeloarchitectonic areas 56–57 cover the Pars opercularis, and were classified as members of the bistriate (area 56) or unitostriate (area 57) group of isocortical areas in the frontal lobe. The unitostriate areas 58–59 found in the Pars triangularis are comparable to BA45. The bistriate area 53 may correspond to parts of BA47 (Figure 2). The unistriate area 41 and ventral parts of area 40 match the position of the oro-facial region, which are comparable to the ventral part of Brodmann’s area 6 [7].

BA44 can further be subdivided into an antero-dorsal (44d) and a ventro-posterior (44v) part based on mapping of receptors for neurotransmitters [41], and functional neuroimaging studies. The dorsal part of left BA44, which seems to correspond to 44d, was shown to be involved in phonological processing during acoustic presentations if single phonemes [33]. Phonological decoding in both hemispheres would then occur via callosal connections [34]. Another study demonstrated that 45a and 45p are differentially involved in sentence processing [35], thus supporting the notion of cortical segregation within BA45. Areas of Broca’s region are central for processing syntactic dependencies between elements of a sentence [36]. Decisions on syntactic properties of single words result in activations of the left BA44 and BA45 [37], which may be caused by challenging the syntactic working memory [38]. Both areas are also required in prosodic decoding [39,40]. Sign language leads to an activation of the left BA45 [41]. Left BA45 is more extensively activated than left BA44 if words must be selected and generated belonging to semantic categories compared to over-learned words, which would not require a major semantic effort [42]. The semantic processing in BA45 is also supported by the finding that the left BA45 is more involved in semantic processing than the left BA44, which is more active in syntactic processing [43]. An extension of Broca’s region beyond the opercular and triangular parts of the inferior frontal gyrus in the light of functional data was discussed as well [44*,45*].

The multimodal investigation of the distribution patterns of multiple receptors and cytoarchitectue points into the same direction [46*,47*]. New areas were identified at the junction of the inferior frontal sulcus (if) and the ventral precentral sulcus (pci), where premotor area BA6 is located.

It was also suggested that the oro-facial part of the ventral precentral gyrus extending posteriorly to the anterior subcentral sulcus belongs to Broca’s region [48,49,50**]. This region contains areas overlapping with parts of the premotor cortex, and eventually the primary motor cortex (BA4) [46**,47*]. Vento-caudal area 6VC resembles FB, and ventro-rostral area 6VR FA of von Economo and Koskinas [23**]. The orofacial part of the agranular BA4 contains much smaller Betz cells than its hand and trunk representation, while the agranular BA6 does not contain Betz cells. The orofacial part of the premotor cortex has been identified more than 70 years ago using functional observations during surgery [51,52]. The role of the premotor cortex for planning of speech and categorization was later supported by functional imaging observations and intraoperative mapping [53,54]. The premotor cortex also contributes to expressive language [55]. The left the premotor cortex of right-handers and
the right the premotor cortex of left-handers are activated during lexical decisions on manual-action verbs like ‘grasp’ or ‘throw’, indicating a representation of action verb semantics from an egocentric perspective [56]. It has been suggested that understanding of nouns for graspable objects requires ‘body-based’ experience [57], and similar neural mechanisms as those enabling grasping [58]. Thus, processing of those nouns seems to engage classical Broca areas and the premotor cortex.

Similar to other brain regions [59, 60], the inferior frontal gyrus shows a highly differentiated regional and laminar distribution of multiple transmitter receptors (Figure 3). Multi-receptor fingerprints, indicating the interrelationship...
of receptor concentrations for different neurotransmitters in various areas, show a relatively high degree of similarity of areas involved in language processing [59], but also point to differences in signal processing in each area (Figure 4). The fingerprints also suggest the subdivision of BA44 and BA45. They allow to identify laminar receptor concentrations of those receptors, which most contribute to the subdivisions. For example, there is a lower concentration of 5-HT2 receptors in 44d than in 44v, while other receptors show similar concentrations. BA45 consists of an anterior (45a) and a posterior (45p) part with higher mean (averaged over all cortical layers) concentrations of some glutamate, GABA, acetylcholine and serotonin receptors in 45a than 45p [46]. AMPA receptor concentrations are higher in the supragranular layers, and those of α1 receptors in the deeper layers of 44d than 45p [46**]. Furthermore, 45a differs from the dorsally located prefrontal area BA46 by lower AMPA and GABA_A, but higher NMDA and M2 receptor densities [61**].

BA47 differs from BA44 and BA45 by higher concentrations of AMPA, kainate, GABA_A, GABA_B, α1, α2, and particularly 5-HT1A receptors at the orbitofrontal part of the inferior frontal gyrus receptors (Fig. 3). The fingerprints of ifs and ifj areas are more similar to that of 45p than to those of 44v, 44d, 45a and BA47 as shown by a hierarchical cluster analysis (Figure 4). Whereas nearly all receptors reach highest concentrations in layers II–IV of all these areas, the glutamatergic kainate and nicotinic α4/β2 have their maxima in layers V–VI or layer IV, respectively. BA44 and 45 are separated by ifs from prefrontal areas BA 46, 8 and 9 [7*].

The ifs has often been interpreted as a landmark between the functionally distinct ventro-lateral prefrontal cortex including Broca’s region, and the dorso-lateral prefrontal cortex. However, multi-receptor analysis and fMRI studies challenge the concept of a simple bi-partition of the prefrontal cortex. Novel areas (areas ifj1 and ifj 2) were detected at the junction of the inferior frontal with the precentral sulcus, and within the adjacent inferior frontal sulcus (areas ifs1 to ifs4) in a multi-receptor study [46*,62]. Areas ifj1 and ifj2 neighbor 44d, and are also dysgranular in their cytoarchitecture. Ventro-posteriorly, 44v has a border with the premotor area 6v1 (Figure 5a). Areas ifj1 and ifj2 may represent the receptorarchitectonic correlates of the functionally identified inferior frontal junction region, which has been reported to be involved in task switching [63–65] but also color and motion attention [66]. Area 44d differs from ifj1 by higher glutamate AMPA, acetylcholine muscarinic M2, and GABA_A receptor densities, while area 45p shows higher kainate and M2 receptor densities than dorsally adjacent ifs1 [46**,62]. In a functional imaging study of Makuuchi et al. [67] on oral working memory, three activation
clusters were found within the left ifs: an anterior (LIFSa), a middle (LIFSm) and a posterior (LIFSp) cluster. These findings support the existence of a rostro-caudal organization of areas within the ifs, which corresponds to a receptor study [62]. Thus, areas in the inferior frontal sulcus may contribute to Broca’s region, extending the classical view of only BA44 and 45. Ventral to area 44v, areas op8 and op9 were discovered on the frontal operculum [46**]. A role of the frontal operculum for language has been described for processing local transitions as compared to hierarchical dependencies [68]. Area op8 contains higher AMPA, GABA_B, M_2, α_1,
Comparison of sulcal patterns between human, bonobo (Pan paniscus), common chimpanzee (Pan troglodytes), gorilla (Gorilla gorilla), orangutan (Pongo pygmaeus), gibbon (Hylobates lar), and baboon (Papio hamadryas) brains in lateral views of the frontal lobe. a, ascending sulcus (violet); c, central sulcus (red); d, diagonal sulcus (violet); fm, frontomarginal sulcus; h, horizontal sulcus (violet); iar, inferior branch of the arcuate sulcus (black); if, inferior (green) frontal sulcus; ipd, intraparietal sulcus (blue); if, lateral fissure (pink); lo, lateral orbital sulcus (white); mf, middle frontal sulcus (white); o, orbital sulci (white); of, orbitofrontal sulcus (blue); p, principal sulcus (black); pci, inferior part of the precentral sulcus (yellow); pcs, superior part of the precentral sulcus (yellow); sar, superior branch of the arcuate sulcus (black); sca, anterior subcentral sulcus (red); scp,
α₃ and 5-HT₁₄, but lower kainate and GABA_A receptor densities than 44v. Area op9 is located rostral to op8 and ventral to 45a. The latter area shows lower kainate, α₁ and 5-HT₂, but higher NMDA, GABA_B, M₂, and M₃ receptor densities than op9. Areas op8 and op9 are in close neighborhood to the insular areas, which have been related to motor aspects of speech [69].

Finally, areas 6v1, 6v2 and 6r1 were identified in the precentral sulcus posterior to dysgranular areas 44v and 44d, and anterior to the primary motor cortex, BA4 [46**]. 6r1 differs from the 6v1 and 6v2 by an extremely thin and discontinuous layer IV. Area 6r1 shows higher M₂ and α₁ receptor densities than BA6 [46**].

Interhemispheric differences

Lateralization is a central question to any study on Broca’s region [70], and structural asymmetries were interpreted as putative correlates of functional lateralization and dominance for language [5,71*]. Volumes of left BA 44 show a consistent left-larger-than-right interhemispheric difference [26**,72–74], while the difference did not reach significance in BA45. In addition to volume, cytoarchitectonic features (e.g. volume fraction of cell bodies in different layers) differ between left and right BA44 and BA45. The somata of the largest layer III pyramidal neurons of left BA45 were significantly larger [75,76] and had a larger dendritic length [75] than those of the right BA45. The total number of neurons was significantly higher in left BA44 of the five male brains, and higher — although not significantly — in left BA45 of the five female brains [77].

The arcuate fascicle (for more details see next paragraph) showed a leftward lateralization in ~60% of human brains. Only ~20% of the brains had a symmetric arcuate fascicle, and the rest a mild leftward lateralization [78]. In contrast to its lower lateralization in female brains, 85% of the arcuate fascicles were left-lateralized in male brains. The prevalence of leftward asymmetry in the direct segment of the arcuate fascicle in right-handers is more pronounced than that of the Planum temporale, a region that was often selected as most prominent example for lateralization [79]. Considering the >90% left-hemispheric functional dominance of language in right handers, the asymmetry of the arcuate fascicle represents the most conspicuous structural sign of language lateralization.

Interhemispheric differences in the densities of transmitter receptors between ventral prefrontal (areas 44, 45, 47, op8, op9) and ventral motor and premotor areas (4, 6) were mainly caused by the muscarinic M₂ receptors. Within the sample of analyzed areas, particularly BA44, but also BA45 and areas 6v1, and 6r1 differ between the hemispheres with higher receptor concentrations in left than in the right [46**].

Relationship of cortical areas to sulcal landmarks

The relation between BA44 and BA45 to surrounding sulci varies between brains and hemispheres [26**,42], and is additive to intersubject variability in the sulcal pattern of this region [26**,42]. For example, the border between both areas was coincident with the diagonal sulcus (d) in some hemispheres, or was completely absent (in about 50% of the hemispheres), or was found completely within BA44 [26**,42]. The latter topographical relationship was the reason to suggest a subdivision of BA4 into two areas [23**]. The posterior border of BA44 to BA6 was found on the anterior, in other cases on the posterior wall of the pce. The position of this border varies between brains by a geodesic distance of 15–20 mm. Similar variation has been found in relation to superior and inferior walls of the ifs, but BA44 and BA45 never extended to the free surface of the medial frontal gyrus [26**], which makes this sulcus a good estimate for the dorsal extent of BA44 and 45. Apart from this, the macroscopic landmarks around and within Broca’s region are not precise indicators of the borders between BA44 and BA45. Their intersubject variability is considerable [8,80,81], which is of growing importance for brain mapping, since modern MR scanners allow a spatial resolution below 1 mm.

Interindividual variability and probabilistic mapping

Probability maps of cytoarchitectonically defined cortical areas are a tool to localize in vivo functional neuroimaging data with respect to the underlying microstructural segregation (Figure 5). These maps represent interindividual variability in a common standard reference space [26**,42], and inform on the probability with which a cytoarchitectonic areas can be found at an actual position. Such maps are accessible for the research community (e.g. https://www.jubrain.fz-juelich.de/apps/cytoviewer/cytoviewer-main.php#); they are also part of the human brain atlas of the European Human Brain Project (https://www.humanbrainproject.eu/en/explore-the-brain/atlas/) and other, publicly available sources, for example, the SPM Anatomy toolbox (http://www.fz-juelich.de/imim/imim-1/DE/Forschung/docs/SPMANatomyToolbox/SPMANatomyToolbox_node.html), FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), or the scalable brain map...
The inferior frontal and precentral sulci can easily be identified in the bonobo, common chimpanzee, gorilla and orangutan brains [83,84,85,86–89]. Homologues of both sulci are not found in gibbon, baboon and macaque brains, which instead contain an arcuate and a principal sulcus in the frontal lobe not seen in the human and great ape brains (Figure 6). An orbitofrontal sulcus is visible in all ape, baboon and macaque brains with the exception of the human brain (Figure 6). Thus, this sulcus represents a notable difference between ape and human brains, and is an important landmark for studies of endocasts in palaeoneurology.

Comparisons between sulci and the borders of the cytoarchitectonically defined areas 44 and 45 reveal that they do not precisely match in human [26**] or ape brains [85**,86–89]. However, similarities in cytoarchitecture, position in the inferior frontal lobe and shared non-language related functions (e.g. orofacial expressions, mirror neurons in the macaque premotor area F5 responding to communicative mouth gestures) have led to an identification of area 44 in various non-human primates [85**,86–94]. Notably, it has been proposed that simulation of motor acts as found in F5, caudally adjacent to area 44, may facilitate communication [95**]. Deep layer III and layer V of macaque area 44 contain very large or mediumsized pyramidal cells. Its layer IV is inconspicuous [94,96]. Therefore, area 44 of macaques can be classified as dysgranular cortex. Layer III of macaque area 45 is similar to that of area 44 by the occurrence of clusters of very large pyramidal cells in its deeper part. These pyramids are even larger than those in layer V. In contrast to area 44, area 45 has well-developed layer IV (granular cortex), and its layer V consists of a layer Va with medium-sized pyramidal cells and a cell-sparse layer Vb as a border region adjoining layer VI. Thus, the macaque map of Walker [97] must be revised, because he missed area 44, and the largest part of Petrides’ area 45 [94] is occupied by the posterior half of Walker’s area 46.

However, it is problematic to assume such homologies by comparing only the relatively distantly related macaques with humans. Instead we must perform additional studies of the cytoarchitecture and connections in our nearest relatives, that is, the bonobo and common chimpanzee and the other apes.

Species-specific, volitional calls and vocalizations of non-human primates require the ventral auditory pathway, which is also found in humans [98–103], and connects the superior and middle temporal gyrri with cytoarchitectonic areas anterior and below area 44. These regions are putative homologues of human BA45 and BA47 in non-human primates [50**,93]. Thus, this and the more dorsally located and evolved arcuate fasciculus pathway [101,104,105], together with the cortical areas as sources and targets of this pathway may have undergone further differentiation for the processing of verbal information in humans. Accordingly, the wider spaced minicolumns of human BA44 and BA45 compared to areas 44 and 45 in non-human primates [106**] indicates the availability of more space for neural connections. A leftward asymmetry
and expanded connections with the middle and inferior temporal gyri compared to the great apes are further indicators of this differentiation.

In summary, the Broca region of non-human primates seems to have cortical areas with largely similar cytoarchitecture and connections comparable to those in the human language system. But how could humans develop a complex language on the basis of neuroanatomical conditions principally not different from those of non-human primates? The mechanism could be neural reuse specified as the ‘massive redeployment’ hypothesis by Anderson [107,108**] for evolutionary processes, or as the ‘recycling theory’ by Dehaene [109**] for developmental processes. Since the cultural environment is one important factor for functional differentiation and evolutionary history of the human brain, the development of language, reading and writing may be enabled by epigenetic/plasticity processes. These processes are driven by the specific cultural challenges without the genetically based re-programming for which the time span of cultural evolution is too short. This was conceptualized as ‘cultural neural reuse’ [110**], and may explain the phenotypic modifications of cortical areas in the human inferior frontal gyrus during brain evolution and individual development. Cultural neural reuse may lead to plastic reactions in the functionally less specialized areas in the inferior frontal gyrus of non-human primates. This epigenetic differentiation was interpreted as an extended case of epigenesis as proposed by D’Ambrosio and Colage® [110**].

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Conflict of interest statement
Nothing declared.

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