

**REVIEW**

Microsurgical anatomy of language

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Abstract

The localizationist model, which focused on classical cortical areas such as Broca's and Wernicke's, can no longer explain how language processing works. Over recent years, several studies have revealed new language-related cortical and subcortical areas, resulting in a transition from localizationist concepts to a hodotopical model. These studies have described language processing as an extensive and complex network of multiple interconnected cortical areas and subcortical pathways, differing from the classical circuit described by the localizationist perspective. The hodotopical model was made possible by a paradigm shift in the treatment of cerebral tumors, especially low-grade gliomas: total or subtotal tumor resections with cortical and subcortical mapping on awake patients have become the gold standard treatment for lesions located in the dominant hemisphere. In this article, we review current understating of the microsurgical anatomy of language.

KEYWORDS

anatomy, brain plasticity, hodotopy, language

1 | INTRODUCTION

A solid understanding of topographic anatomy is a crucial principle of tumor resection in neuro-oncology. Yasargil (1994) and Rhoton (2007) described the microsurgical anatomy of the nervous system. Although several other microsurgical studies have described classical language areas accurately, this localizationist model cannot consistently provide an ideal representation of the anatomical basis of language processing.

A more accurate understanding of this subject has become possible thanks to recent publications on brain plasticity (Duffau, 2005, 2009, 2014; Duffau, Capelle, Denvil, Sichez, et al., 2003; Thiel et al., 2001), glioma re-operations in language areas (Martino, Taillandier, Moritz-Gasser, Gatignol, & Duffau, 2009), and cortical and subcortical brain mapping (Bello et al., 2007; Catani, Dell'Acqua, Bizzi, et al., 2012; Catani, Jones, & Ffytche, 2005; De Benedictis et al., 2014; De Benedictis, Sarubbo, & Duffau, 2012; Duffau, 2007; Duffau, 2015; Duffau et al., 2002; Duffau, Leroy, et al., 2008; Duffau, Peggy Gatignol, et al., 2008; Duffau, Thiebaut De Schotten,

et al., 2008; Matsumoto et al., 2004; Tarapore et al., 2012). Because of this shift from a localizationist to an associativist viewpoint, not only the major tracts and cerebral fasciculi, but also the whole cortex must be reviewed. The goal of the present study is to review the microsurgical anatomy of language in conformity with emerging concepts of hodotopy (Catani, 2007; Catani & ffytche, 2005; De Benedictis & Duffau, 2011; Duffau, 2008; Duffau, 2015; Duffau, Capelle, Denvil, Gatignol, et al., 2003).

2 | SUPPORTING DISSECTION MATERIAL

To illustrate this review, we added figures of hemispheric dissections. Twelve brain hemispheres were collected from autopsies and fixed in 10% formalin for about 4 weeks. Caution was required to prevent deformations caused by incorrect storage positions. Following the fixation period, the brains were frozen at -12°C for another 4 weeks. Ten of the formalin-fixed human brains were dissected using $\times 3$ to $\times 40$ surgical microscope magnification. One of the authors (G. R. I)

performed the dissections at the Dianne and Gazi Yasargil Education Center, University of Arkansas for Medical Sciences.

To enhance vessel visibility, we injected colored silicone into the other two brains. On the 10 (not silicone-injected) brains, we performed fiber dissections according to Klinger's method. First, we identified the sulci and gyri on the lateral surface of each brain. Then the cortex was peeled, exposing the short-association fibers (U-fibers). As the dissection progressed, we identified and separated the tracts and fasciculi according to previous descriptions (Rubino, Rhoton, Tong, & De Oliveira, 2005; Sincoff, Tan, & Abdulrauf, 2004; Türe, Yaşargil, Friedman, & Al-Mefty, 2000).

2.1 | Topographic anatomy of language—cortical areas

Classical language areas such as Broca's and Wernicke's areas do not have the exact functions attributed to them decades ago (Benzagmout, Gatignol, & Duffau, 2007; De Benedictis, Moritz-Gasser, & Duffau, 2010; Maldonado et al., 2011; Martino et al., 2009; Plaza, Gatignol, Leroy, & Duffau, 2009; Sarubbo, Le Bars, Sylvie, Duffau, & Sarubbo, 2012; Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2014). A connectionist model has recently replaced the classical principle of localizationism (Catani, 2007; Catani & ffytche, 2005; De Benedictis & Duffau, 2011; Duffau, 2008; Duffau, 2015; Duffau,

Capelle, Denvil, Gatignol, et al., 2003). This new hodotopical model perceives language as a system of integrating networks. Each network is composed of hubs and pathways connecting the areas involved.

2.1.1 | Broca's area

Conventionally, this area is located in the inferior frontal gyrus (Figure 1a). The posterior limit of the frontal lobe is the central sulcus, which has a vertical orientation. The precentral sulcus is parallel to the central sulcus and delimits the precentral gyrus. Anterior to the precentral gyrus, the frontal lobe is divided into three portions (superior, middle, and inferior gyri) by the superior and inferior frontal sulci, which are perpendicular to the precentral sulcus (Figure 1a).

The anterior horizontal, anterior ascending, and posterior rami of the lateral sulcus (also called the Sylvian fissure) divide the inferior frontal gyrus into three portions: pars orbitalis, pars triangularis, and pars opercularis (Figure 1a). The apex of the pars triangularis is directed inferiorly toward the junction of the three rami of the lateral sulcus. This point coincides with the anterior limiting sulcus of the insula. The pars orbitalis, pars triangularis, pars opercularis, and precentral gyrus form the frontal operculum of the lateral sulcus. They are related inferiorly to the planum polare in the temporal lobe (Figure 1a). Broca's area is the region composed of the pars triangularis and the pars opercularis of the dominant hemisphere.

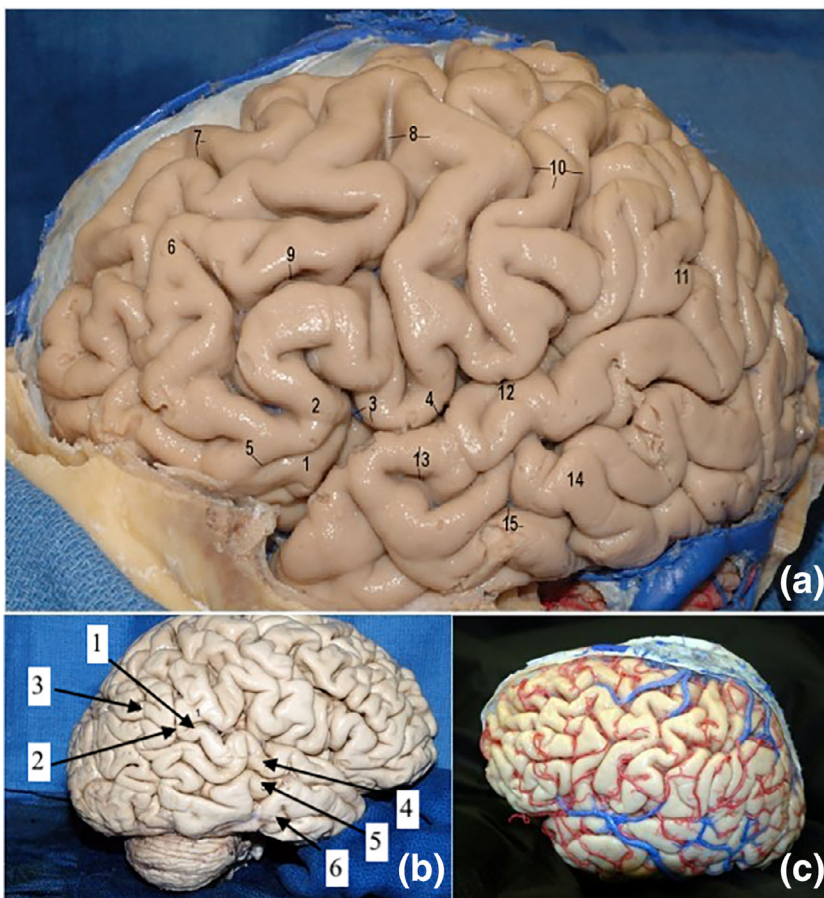


FIGURE 1 Surface anatomy of the cerebral hemispheres. (a) Lateral surface of the left hemisphere. 1. Pars orbitalis; 2. Pars triangularis; 3. Ascending ramus of the lateral sulcus (Sylvian fissure) and pars opercularis; 4. Posterior ramus of the lateral sulcus; 5. Anterior horizontal ramus of the lateral sulcus; 6. Middle frontal gyrus; 7. Superior frontal sulcus and superior frontal gyrus; 8. Precentral sulcus and precentral gyrus; 9. Inferior frontal sulcus; 10. Central sulcus, postcentral gyrus and postcentral sulcus; 11. Supramarginal gyrus; 12. Transverse temporal gyrus (Heschl's gyrus); 13. Superior temporal sulcus and gyrus; 14. Middle temporal gyrus; 15. Inferior temporal gyrus. (b) Posterolateral view of the right hemisphere. 1. Supramarginal gyrus; 2. Angular gyrus; 3. Intraparietal sulcus and superior parietal lobule; 4. Superior temporal gyrus; 5. Middle temporal gyrus; 6. Inferior temporal gyrus. (c) Lateral view of the left hemisphere with arterial and venous preservation [Color figure can be viewed at wileyonlinelibrary.com]

Broca's area is classically related to expressive aphasia and is frequently referred to as the motor area of speech. On the other hand, the inferior frontal gyrus of the nondominant hemisphere is associated with prosody, the capacity to express emotions through modulation of speech rhythm and intonation (Catani, Dell'Acqua, Bizzi, et al., 2012).

Classical Broca's aphasia (or nonfluent aphasia) can be caused by lesions outside Broca's area such as the postcentral parietal regions. Dysfunction of Broca's area can result from injuries to its connections with posterior and temporal language areas, and stimulation of Broca's area rarely leads to suppression of speech output.

However, this symptom has been consistently related to ventral premotor cortex stimulation (Tate et al., 2014), and the final common speech output hubs seem to be the bilateral ventral premotor cortices (Figure 1a). Stimulation of the precentral gyri on both sides, particularly in their posterior regions, causes complete cessation of speech output. In contrast, impaired ability to express emotions through the modulation of speech intonation, rhythm, and gestural expression is more often observed in injuries to the inferior frontal gyrus of the nondominant hemisphere (Tate et al., 2014).

2.1.2 | Wernicke's area

Wernicke's area is classically related to comprehension or fluent aphasia. It is called fluent aphasia because a person afflicted with it can express words fluently, yet without meaning. Although this area has been defined as the posterior superior temporal gyrus (Figure 1a,b), other nearby regions have also been considered as part of Wernicke's area during the past 15 years. They are the angular gyrus, supramarginal gyrus, middle temporal gyrus, and posterior superior temporal sulcus (Figure 1b).

On its lateral surface, the temporal lobe is limited superiorly by the posterior ramus of the lateral sulcus and posteriorly by the parietotemporal and occipitotemporal lines. It is divided into three main gyri (superior, middle, and inferior) by two main sulci (superior and inferior temporal; Figure 1a,b). The parietal lobe is limited inferiorly by the lateral sulcus and the occipitotemporal line, anteriorly by the central sulcus, medially by the longitudinal cerebral fissure and posteriorly by the parietotemporal line. It has two main sulci, the postcentral and intraparietal. The intraparietal sulcus splits the lateral surface of the parietal lobe into superior and inferior parietal lobules.

The inferior parietal lobule has two gyri, the supramarginal and the angular (Figure 1b). The supramarginal gyrus is the posterior continuation of the superior temporal gyrus and wraps around the posterior ramus of the lateral sulcus. The angular gyrus is the posterior continuation of the middle temporal gyrus and turns in a superomedial direction behind the posterior ramus of the lateral sulcus (Figure 1b). Therefore, Wernicke's area is not precisely delimited, since it covers the posterior superior temporal sulcus and the angular, supramarginal, and middle temporal gyri of the dominant hemisphere.

Wernicke's aphasia, characterized by impaired auditory comprehension, repetition, and normal verbal fluency, is related to injuries to

the posterior segment of the arcuate fasciculus (AF; Catani et al., 2005; Catani, Dell'Acqua, Bizzi, et al., 2012). Injuries to the nondominant side are related to impairments of the emotional aspects of language and music (Catani et al., 2005; Figures 2a,b, 4c, 5b, 6b, and 7a,b). The inferior parietal lobe, also known as Geschwind's territory, is involved in the analysis of phonological and temporal aspects of words. Some authors have speculated that the angular gyrus is partially responsible for the understanding of metaphors (Tremblay & Dick, 2016).

2.1.3 | Exner's area

Exner's area, located in the middle frontal gyrus (MFG), has been considered the writing center since the nineteenth century. The MFG is limited superiorly by the superior frontal sulcus, inferiorly by the inferior frontal sulcus and posteriorly by the precentral sulcus (Figure 1a). Exner's area is the posterior portion of the MFG, adjacent to the precentral sulcus and anterior to the primary motor area of the hand in the precentral gyrus.

2.1.4 | Cerebellum

The cerebellum is located posterior to the brain stem in the posterior cranial fossa. It has a medial portion, the vermis, and two great lateral masses, the hemispheres, and is connected to other structures by the cerebellar peduncles. The superior cerebellar peduncle connects the cerebellum to the cerebrum, the middle cerebellar peduncle connects it to the pons, and the inferior cerebellar peduncle connects it to the medulla oblongata and the olivary nucleus. Internally, there are four paired nuclei of gray matter: dentate nucleus, emboliform nucleus, globose nucleus, and fastigial nucleus. These central nuclei receive fibers from the cerebellar cortex and send fibers to the cerebrum.

The cerebellum has both motor and nonmotor functions in language. Cerebellar functions involving motor coordination have long been established as essential for the control of articulation and clarity of speech through the oropharyngeal vocal apparatus, dysfunctions of which present as dysarthria.

However, only in recent decades has the nonmotor role of the cerebellum in language been studied more thoroughly (Ackermann, 2013). The cerebellum modulates higher-order cognitive processes, contributing to other aspects of language such as motor speech planning, verbal working memory, syntax processing, phonological and semantic verbal fluency, reading, and writing (Beaton & Mariën, 2010; De Smet et al., 2013; De Smet, Baillieux, De Deyn, Mariën, & Paquier, 2007; Gordon, 1996; Highnam & Bleile, 2011; Mariën et al., 2014; Mariën, Engelborghs, Fabbro, & De Deyn, 2001; Murdoch, 2010; Paquier & Mariën, 2005).

Neuroimaging studies have demonstrated that the sensorimotor cerebellum is associated with regions in the anterior lobe, extending into medial lobule VI and lobule VIII, while the neurocognitive cerebellum is associated with regions in the posterior lobe, namely lobules VI

and VII (Buckner, Krienen, Castellanos, Diaz, & Thomas Yeo, 2011; Habas et al., 2009; Stoodley & Schmahmann, 2009). Nonmotor language functions are frequently located in the posterior cerebellar lobe of the nondominant hemisphere. This lateralization reflects a link between the cortical language network and the cerebellum, subserved by crossing cerebellar-cerebral connections. This anatomical dichotomy between motor and nonmotor cerebellum is also observed in the cerebellar nuclei.

In some imaging studies, the cerebellar motor functions have been related to rostral parts of the dentate nuclei, while nonmotor cerebellar functions have been assigned to the ventrocaudal parts of the dentate nucleus of the nondominant hemisphere (Thürling et al., 2011). The emboliform and globose nuclei are related to motor speech control because paravermal injuries are often followed by dysarthria.

2.1.5 | Basal ganglia

The basal ganglia are telencephalic structures composed of gray matter nuclei in the central core, which are laterally covered by the insula. They are composed of the striatum, the globus pallidus, the substantia nigra, and the subthalamic nucleus. The striatum is divided into the caudate nucleus, putamen, and nucleus accumbens (Figures 2a,b,3a,b, and 4b).

The caudate nucleus is a large structure closely related to the lateral ventricles throughout their extent. The head is its anterior extremity, contiguous with the anterior part of the lentiform nucleus, and forms the lateral walls of the frontal horn. The body is in the

central portion of the lateral ventricle. The tail describes a posteroinferiorly-directed curve, extending from the atrium into the roof of the temporal horn, and is contiguous with the amygdaloid nucleus (Figures 2a and 3a,b).

The putamen and the globus pallidus form the lentiform nucleus, and a thin layer of white matter separates them. Lateral to the insula, the lentiform nucleus is separated medially from the caudate nucleus and the thalamus by the internal capsule. The putamen is larger than the globus pallidus and lateral to it. The nucleus accumbens is a gray matter structure located between the head of the caudate nucleus and the putamen (Figures 2a, 3a, and 4b). These areas are also related to language function (Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005).

2.2 | Cortical hubs

A hub is a functional epicenter that allows multiple data from unimodal systems to be integrated multimodally (Duffau, Herbet, & Moritz-Gasser, 2013).

2.2.1 | Visual word form area and visual object form area

The visual word form area (VWFA), so called because of its role in the visual word form system, is located in the dominant fusiform gyrus. The VWFA seems to be involved in the first stage of the reading process (Cohen et al., 2000). It receives visual input from the occipital cortex through the lower fibers of the posterior part of the inferior

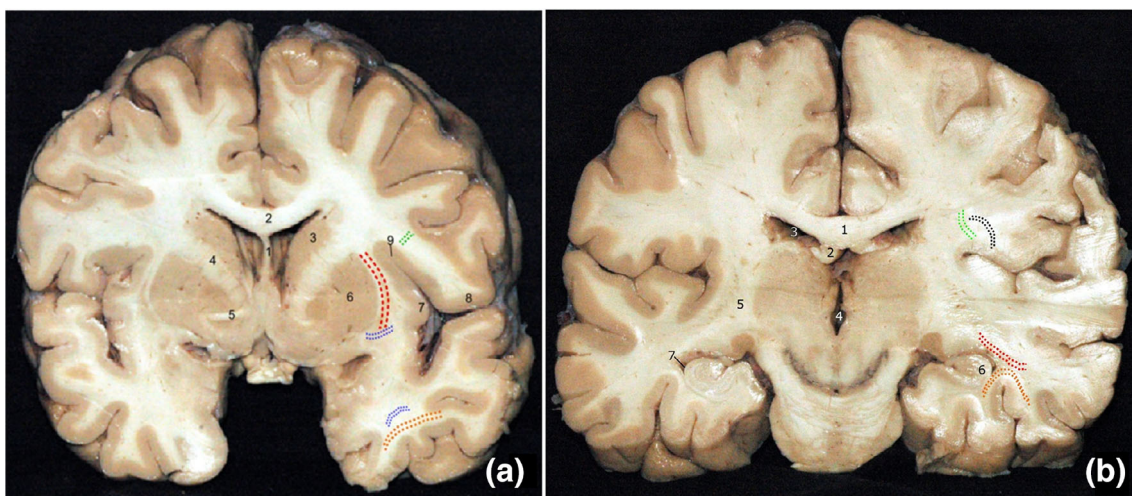


FIGURE 2 Coronal view of the brain. (a) Coronal view with long association fiber representation. 1. Septum pellucidum; 2. Corpus callosum; 3. Caudate nucleus; 4. Internal capsule; 5. Anterior commissure; 6. Lentiform nucleus; 7. Insular compartment; 8. Opercular compartment; 9. Superior limiting sulcus; arcuate fasciculus (green); inferior occipitofrontal fasciculus (red); uncinete fasciculus (blue); inferior longitudinal fasciculus (orange). (b) Coronal view with long association fiber representation. 1. Corpus callosum; 2. Fornix; 3. Lateral ventricle; 4. Third ventricle; 5. Internal capsule; 6. Hippocampus; 7. Temporal horn of the lateral ventricle; superior longitudinal fasciculus III— anterior segment (black); arcuate fasciculus (green); inferior occipitofrontal fasciculus (red); inferior longitudinal fasciculus (orange) [Color figure can be viewed at wileyonlinelibrary.com]

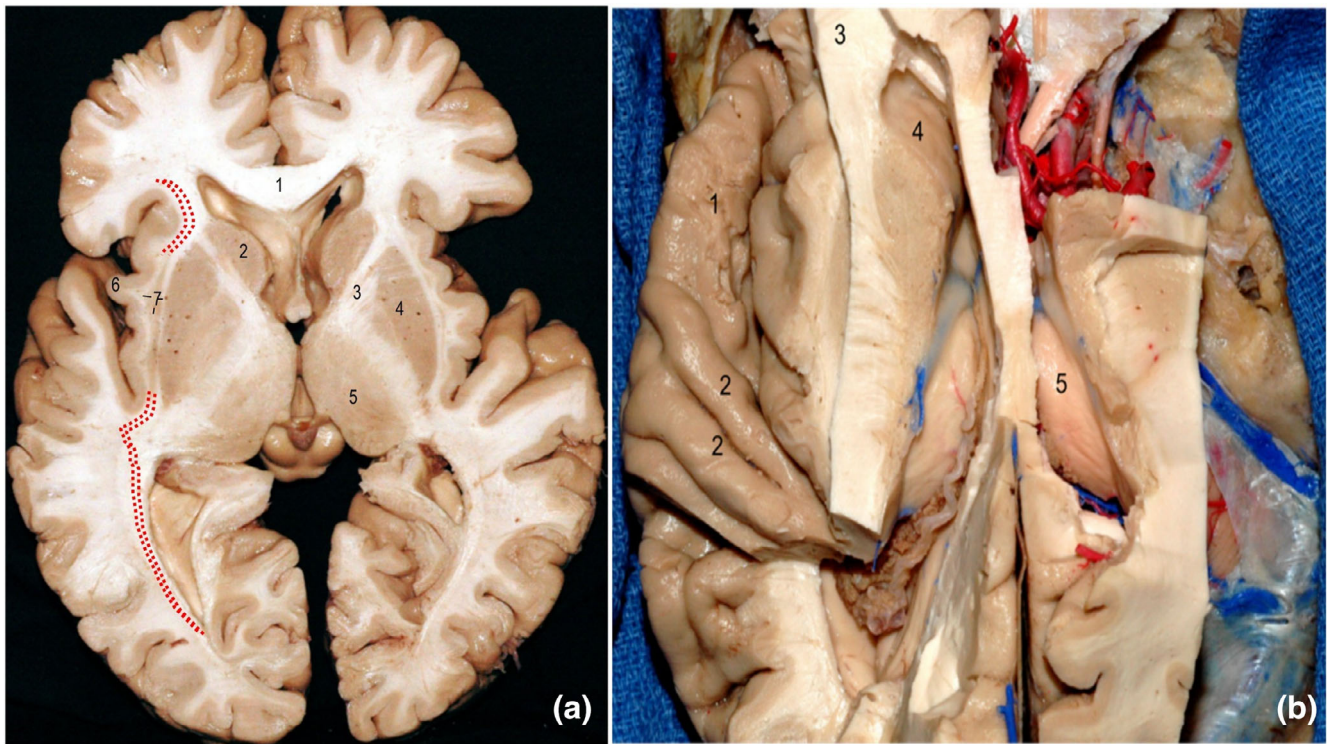


FIGURE 3 Axial view of the brain. (a) Axial view with long association fibers representation. 1. Genu of the corpus callosum; 2. Head of the caudate nucleus; 3. Internal capsule; 4. Lentiform nucleus; 5. Thalamus; 6. Insular cortex; 7. External capsule, claustrum and extreme capsule; inferior frontal occipital fasciculus (red). (b) Axial view. 1. Planum polare; 2. Transverse temporal gyrus (Heschl's gyrus); 3. Corpus callosum; 4. Head of the caudate nucleus; 5. Thalamus [Color figure can be viewed at wileyonlinelibrary.com]

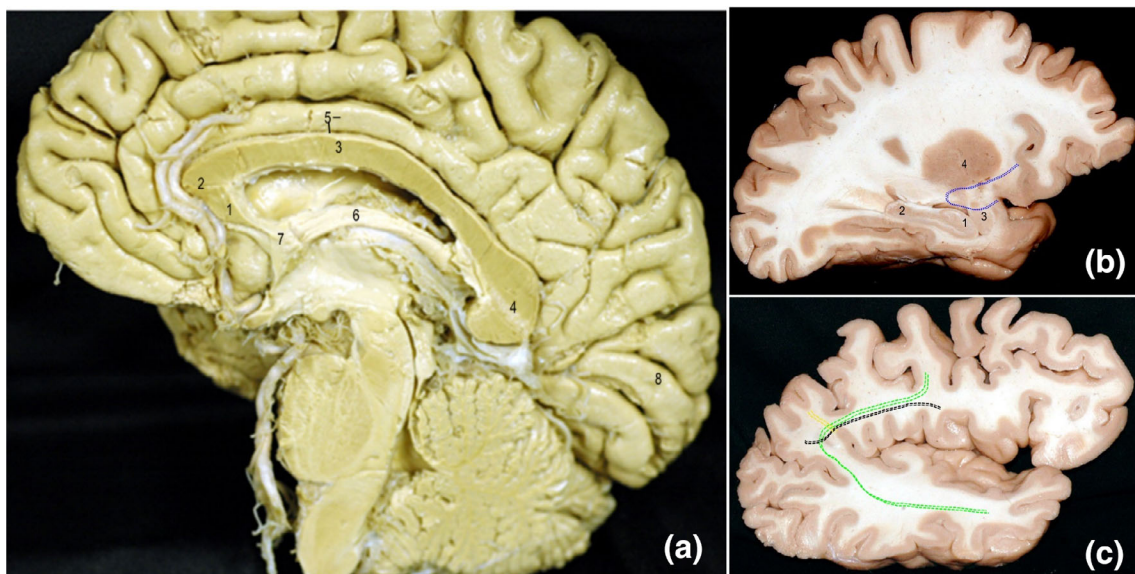


FIGURE 4 Sagittal view of the brain. (a) Medial sagittal view. 1. Rostrum of the corpus callosum; 2. Genu of the corpus callosum; 3. Truncus of the corpus callosum; 4. Splenium of the corpus callosum; 5. Sulcus of corpus callosum, cingulate gyrus and cingulate sulcus; 6. Fornix; 7. Anterior commissure; 8. Cuneus. (b) Sagittal view with long association fiber representation. 1. Head of the hippocampus; 2. Tail of the hippocampus; 3. Amygdala; 4. Putamen nucleus; uncinata fasciculus (blue). (c) Sagittal view with long association fiber representation. Superior longitudinal fasciculus III - anterior segment (black); arcuate fasciculus (green); middle longitudinal fasciculus (yellow) [Color figure can be viewed at wileyonlinelibrary.com]

longitudinal fasciculus (ILFp; Duffau, 2015; Zemmoura, Herbet, Moritz-Gasser, & Duffau, 2015).

The visual object form area (VOFA) is adjacent to the VWFA, also in the fusiform gyrus. The VOFA receives visual input from the occipital cortex through the upper fibers of the ILFp. Therefore, it is involved in visual object recognition and the VWFA in visual word recognition (Duffau, 2015).

2.2.2 | Primary auditory cortex

The primary auditory cortex is the transverse temporal gyrus, also known as Heschl's gyrus (Figures 1a, 3b, and 5a). The dominant primary auditory cortex is more associated with the ability to recognize words, while the nondominant primary auditory cortex has the ability to recognize nonverbal sounds (Tate et al., 2014). The transverse temporal gyrus, located in the temporal operculum of the lateral sulcus, runs mediolaterally on the inferior surface of the temporal lobe and connects with the precentral gyrus in the frontal operculum. The transverse temporal gyrus meets the postcentral gyrus in the lateral sulcus, and this point is projected on the same coronal plane as the external acoustic meatus.

2.2.3 | Insula

The insula is located deeply inside the lateral sulcus and can be observed when the lips of the lateral sulcus are widely separated (Figures 2a and 3a). The insula is separated from the opercula by the superior, anterior, and inferior parts of the limiting sulcus (Figure 5a,b). It is the external covering of the central core, which comprises the extreme capsule, the external capsule, the internal capsule, the claustrum, the basal ganglia, and the thalamus (Figures 2a and 3a).

Also called the central lobe, the insula has a pyramidal shape, its apex pointing in the anteroinferior direction. It has a lateral and an anterior surface. The latter comprises the insular pole, the transverse, and the accessory gyri. The insular apex, the limen insulae, is located in the medial portion of the insular pole (Figure 5a,b). The uncinate fasciculus (UF) fibers of the limen insulae are covered by gray matter that extends from the end of the anterior long gyrus, passes through the insular pole, and ends in the posterior orbital gyrus (Figure 2a). The insular gyri are directed superiorly in a radial manner from the limen insulae. The limen insulae limits the carotid cistern medially and the lateral sulcus laterally (Tanriover, Rhoton, Kawashima, Ulm, & Yasuda, 2004; Türe, Yaşargil, Al-Mefty, & Yaşargil, 1999).

The central sulcus of the insula divides its lateral surface into anterior and posterior zones. The anterior zone has three to five short gyri, while the posterior zone is formed by the posterior and anterior long gyri (Figure 5a,b). The role of the insula and peri-insular structures in language processing is now better understood thanks to studies using trans-operative language mapping (Duffau, Moritz-Gasser, & Gatignol, 2009).

2.2.4 | Supplementary motor area and presupplementary motor area

The supplementary motor area (SMA) lies in the medial region of the superior frontal gyrus, rostral to the primary motor cortex. The presupplementary motor area (pre-SMA) is just anterior to the SMA. Inhibitory motor responses were observed after stimulation of the SMA in awake patients (Penfield, 1954), which was later replicated after stimulation of the pre-SMA as well (Luders, Dinner, Morris, Wyllie, & Comair, 1995).

Transitory postoperative speech and motor disorders have been observed after SMA resections in the dominant hemisphere (Krainik et al., 2003). These disorders seem to be temporary because of

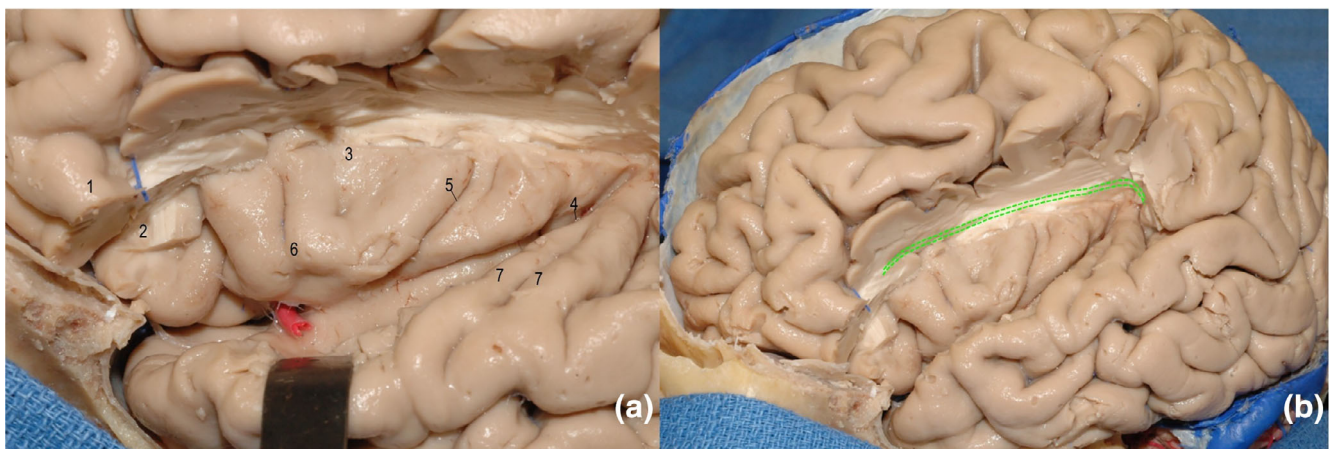


FIGURE 5 Insular view with frontal operculum resection. (a) Frontal operculum resection. Insular view. 1. Pars orbitalis; 2. Anterior limiting sulcus; 3. Superior limiting sulcus; 4. Inferior limiting sulcus; 5. Central sulcus of the insula; 6. Apex of the insula; 7. Transverse temporal gyrus (Heschl's gyrus). (b) Frontal operculum resection. Insular view with long association fiber representation. Arcuate fasciculus (green) [Color figure can be viewed at wileyonlinelibrary.com]

cortical plasticity and recovery has been attributed to the recruitment and activation of the contralateral area (Krainik et al., 2003). Two sub-cortical bundles are related to these areas: the frontal aslant tract (FAT), which connects the pre-SMA to the pars opercularis, and the frontostriatal tract (FST), which connects the SMA to the caudate nucleus (Catani, Dell'Acqua, Bizzi, et al., 2012).

2.3 | Topographic anatomy of language—White matter pathways

White matter consists of myelinated fibers, which are divided into intrahemispheric association, inter-hemispheric association, and projection fibers. Projection fibers connect cortical to subcortical areas, mainly through the fornix and internal capsule (Figures 2a,b, 3a, and 4a). The inter-hemispheric association fibers are the commissural fibers that connect the cerebral hemispheres, namely the commissure of the fornix, the anterior commissure, and the corpus callosum (Figures 2a,b, 3b, and 4a).

Intrahemispheric association fibers connect cortical areas in the same hemisphere and are divided into short (Figure 6a) and long association fibers. The short association fibers connect adjacent gyri, and the long ones, the fasciculi, connect distant gyri. The main fasciculi are the cingulum, the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), the inferior occipitofrontal fasciculus (IOFF), and the UF (Figures 2a,b, 3a, 4a–c, 5b, 6b, and 7a,b).

2.3.1 | Superior longitudinal fasciculus

The SLF is a long bi-directional bundle of neurons connecting parts of the frontal, parietal, occipital, and temporal lobes. The AF is part of the SLF. It arches around the insula after connecting the posterosuperior temporal cortex and the inferior parietal cortex to areas in the frontal lobe. The SLF can be divided into long, anterior, and posterior segments (Martino et al., 2013; Figures 2a,b, 4c, 5b, 6b, and 7a,b).

Diffusion tensor imaging (DTI) tractography and anatomical fiber dissection studies showed that the SLF could be separated into deep and superficial portions (Martino et al., 2011, 2013; Sarubbo, De Benedictis, Milani, et al., 2015). The deep portion corresponds to the classical AF. The superficial portion has two components: the horizontal anterior segment and the vertical posterior segment.

According to Kamali, Flanders, Brody, Hunter, and Hasan (2014), five subcomponents of the SLF have been described. The superior horizontal fibers connect the superior parietal lobe (SLF-I), the angular gyrus (SLF-II), and the supramarginal gyrus (SLF-III) to ipsilateral frontal and opercular areas. The AF is the fourth component and connects the superior temporal gyrus to the ventrolateral prefrontal cortex. The fifth component connects the temporal and parietal lobes and is known as the temporoparietal SLF (SLF TP; Catani et al., 2005; Frey, Campbell, Pike, & Petrides, 2008; Makris et al., 2004; Makris & Pandya, 2009; Zhang et al., 2010).

The anterior segment, also named SLF-III, connects the inferior parietal lobe and the posterior portion of the superior temporal gyrus to the frontal operculum. The posterior cortical terminations of this bundle have been observed in the supramarginal gyrus, in the posterior portion of the superior temporal gyrus and, less frequently, in the angular gyrus.

In the posterior portion of the superior temporal gyrus, the fibers of SLF-III are closer to the auditory radiation originating from the transverse temporal gyrus. These fibers have a posterosuperior orientation, curving around the end of the lateral sulcus, continuing anteriorly and passing along with the parietal and frontal operculum, lateral to the AF. The anterior cortical terminations at the level of the frontal operculum were observed in the ventral portion of the precentral gyrus and, less frequently, in the posterior portion of the inferior frontal gyrus (Martino et al., 2011, 2013).

The posterior segment connects the middle temporal gyrus to the inferior parietal lobe. These fibers have a vertical orientation and pass laterally to the AF. Inferiorly, the cortical terminations were found in the posterior portion of the middle temporal gyrus and, less frequently, in the inferior and superior temporal gyri. The superior

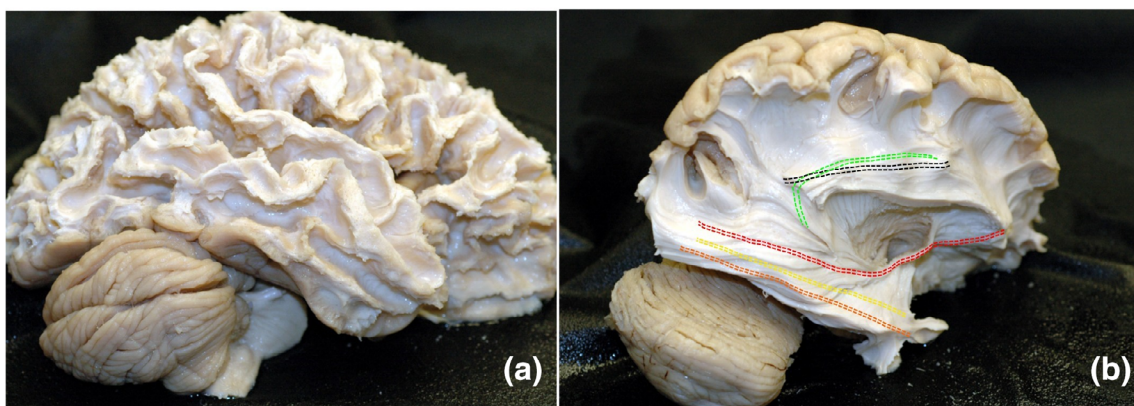


FIGURE 6 Fiber dissection. (a) Short association fibers. (b) Fiber dissection. Long association fiber representation. Superior longitudinal fasciculus III- anterior segment (black); arcuate fasciculus (green); inferior occipitofrontal fasciculus (red); middle longitudinal fasciculus (yellow); inferior longitudinal fasciculus (orange) [Color figure can be viewed at wileyonlinelibrary.com]

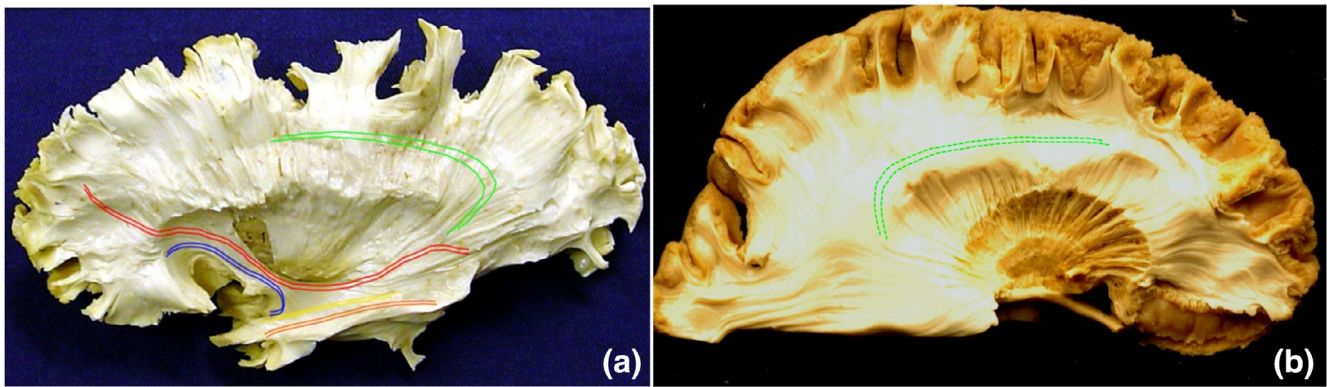


FIGURE 7 Fiber dissection. (a) Fiber dissection. Long association fiber representation. Arcuate fasciculus (green); inferior occipitofrontal fasciculus (red); middle longitudinal fasciculus (yellow); inferior longitudinal fasciculus (orange). (b) Fiber dissection. Long association fiber representation. Arcuate fasciculus (green) [Color figure can be viewed at wileyonlinelibrary.com]

cortical terminations at the level of the inferior parietal lobe were connected to the angular gyrus and, less frequently, to the supramarginal gyrus and the inferior portion of the superior parietal lobe (Martino et al., 2011, 2013).

The AF is a long white matter tract located deeper than the anterior and posterior segments. It is possible to identify the vertically-oriented AF at the level of the middle and inferior temporal gyrus and to separate it from deeper structures. The AF curves around the caudal limits of the insula, taking a horizontal and anterior direction. It runs laterally to the corticospinal tract and reaches the parietal and frontal operculum. The anterior cortical terminations, at the level of the frontal operculum, connect to the ventral portion of the precentral gyrus, to the posterior portion of the inferior gyrus and, less frequently, to the MFG. Posteriorly, the cortical terminations of these fibers are related to the inferior and middle temporal gyri (Martino et al., 2011, 2013).

2.3.2 | Inferior longitudinal fasciculus

The inferior ILF connects the occipital cortex to the lateral occipitotemporal gyrus. Through the lateral walls of the occipital and temporal horns of the lateral ventricle, the ILF also connects the occipital cortex to the temporal pole (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Figures 2a,b, 6b, and 7a).

The ILF is composed of direct and indirect pathways. The direct pathway connects the occipital lobe to the temporal pole, while the indirect pathway is formed by U-shaped fibers, creating an occipitotemporal system (Mandonnet, Gatignol, & Duffau, 2009). The indirect pathway runs inferolaterally to the optic pathways (Mandonnet et al., 2009).

This fasciculus can be divided into posterior and anterior parts. The posterior part of the ILF connects the visual cortex to the VWFA and the VOFA, assisting in the initial stage of language processing. The upper fibers of the posterior part seem to be connected to the VOFA, while the lower fibers are supposedly connected to the VWFA.

The anterior part of the ILF connects the left inferior temporal areas (VOFA) to the temporal pole. Together with the UF, this forms the indirect ventral semantic pathway (Duffau, 2015; Herbet et al., 2016; Mandonnet et al., 2007, 2009).

2.3.3 | Inferior occipitofrontal fasciculus

The IOFF originates from the frontal lobe, connecting it to the occipital cortex, the temporobasal areas, and the superior parietal lobule (Martino, Brogna, Robles, Vergani, & Duffau, 2010). As a single bundle, the IOFF runs along the lateral border of the lentiform nucleus, medial to the corona radiata. It reaches the occipital and temporal lobes, lateral to the temporal and occipital horns of the lateral ventricle (Figures 2a,b, 3a, 6b, and 7a).

Fiber dissection and DTI studies have established the dorsal parieto-occipital and the basal temporo-occipital areas as the posterior origin of the IOFF (Catani, Howard, Pajevic, & Jones, 2002; Martino, Brogna, et al., 2010). Dissection studies have identified the origins of the IOFF in the inferior occipital gyrus, the inferior portion of the middle occipital gyrus, and, to a minimal extent, the lingual gyrus. Two stems were identified in the inferior occipital gyrus. One lies in its anterolateral part, at the border with the inferior temporal gyrus, and the other in a more posteromedial region at the border with the fusiform gyrus (Sarubbo, De Benedictis, Maldonado, Basso, & Duffau, 2013).

In a recent fiber dissection and DTI reconstruction study, two layers of the IOFF were described (Martino, Brogna, et al., 2010; Martino, Vergani, et al., 2010). The superficial layer is anterosuperiorly directed and ends in the inferior frontal gyrus, at the pars triangularis and the pars orbitalis. The deeper layer comprises three portions: posterior, middle, and anterior. The posterior component runs under the junction of the pars triangularis and pars opercularis, ending in the posterior region of the MFG and the dorsolateral prefrontal cortex (DLPFC). The middle component ends in the most anterior part of the MFG and the lateral orbitofrontal cortex (LOFC). The anterior

component is directed toward the basal orbitofrontal cortex and the frontal pole (Sarubbo et al., 2013).

2.3.4 | Uncinate fasciculus

The UF connects the inferior portions of the frontal lobe (such as the orbitofrontal cortex) to the amygdala, the hippocampus and other parts of the limbic system, at the level of the limen insulae (Figures 2a, 4b, and 7a). It also connects the temporal pole to the pars orbitalis. The UF and the anterior part of the ILF form the indirect ventral semantic pathway (Duffau, 2015; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009).

2.3.5 | FAT and FST

The FAT was recently described as an oblique pathway on the coronal plane (Catani, Dell'Acqua, Vergani, et al., 2012; Ford, McGregor, Case, Crosson, & White, 2010; Kinoshita et al., 2015; Oishi et al., 2008). It connects the pre-SMA, in the superior frontal gyrus, to the pars opercularis, in the inferior frontal gyrus (Catani, Dell'Acqua, Vergani, et al., 2012).

A study combining intraoperative electrical mapping and tractography revealed that the FAT takes part in the speech initiation process (Kinoshita et al., 2015). It is left-lateralized in most right-handed subjects, further suggesting its participation in the language process, particularly in verbal fluency (Catani et al., 2013; Catani, Dell'Acqua, Vergani, et al., 2012; Kinoshita et al., 2012; Kinoshita et al., 2015).

The pre-SMA seems to be involved in motor preparation for speech (Nachev, Kennard, & Husain, 2008; Tremblay, Sato, & Small, 2012), while the pars opercularis has been implicated in word selection, language comprehension, word retrieval, and articulation during speech production (Price, 2010). In view of this connection between the pars opercularis and the pre-SMA, the FAT could be involved in speech initiation (Broce, Bernal, Altman, Tremblay, & Dick, 2015; Kinoshita et al., 2015).

The development of the FAT and its relationship with language function were studied in 5- to 8-year-old children. This fasciculus proved to be consistently right-lateralized (Broce et al., 2015), in contrast to the left-lateralized pattern found in adults (Catani, Dell'Acqua, Vergani, et al., 2012). There was evidence of an increase in left laterality with age, which could suggest gradual development (Broce et al., 2015).

The FST, also called the "subcallosal fasciculus" (Duffau et al., 2002), connects the SMA to the anterior part of the caudate nucleus (Kinoshita et al., 2015). From the caudate nucleus, this white matter tract runs around the anterior horn of the lateral ventricle and then follows the ipsilateral FAT. There seems to be an association between the FST and self-initiated movement. Together, the FST and the FAT also seem to be involved in verbal fluency (Kinoshita et al., 2015). It is presumed that they form a negative motor network involved in self-initiated movements and speech processes (Kinoshita et al., 2015).

3 | DISCUSSION

3.1 | Modern study techniques

The advance from a localizationist paradigm to a hodotopical model has been largely driven by modern techniques that allow scientists to study language function *in vivo*. While traditional models were built on evidence from patients with cortical lesions (Berker et al., 1986), current understanding derives from direct electrical stimulation (DES) in awake craniotomies (Duffau, 2015), diffusion tensor imaging and fiber tractography (Kamali et al., 2014), functional MRI (Price, 2010), magnetoencephalography, and navigated transcranial magnetic stimulation (Tarapore et al., 2012). These techniques provide a more accurate insight into the actual organization and functioning of the human brain and will continue to lead research in the yet unclear aspects of language processing.

3.2 | Aspects of language function

Anatomical and tractographical studies (Fernández-Miranda et al., 2008; Türe et al., 2000) have facilitated the identification of white matter tracts involved in language functions. Intraoperative DES provides a unique opportunity to discover the functional roles of cortical hubs and subcortical pathways (Sarubbo, De Benedictis, Merler, et al., 2015).

Dysarthria is related to the lateral precentral and the postcentral gyri on both sides of the brain, suggesting that the sensory system is involved in modulating the articulatory process. Speech articulation is presumed to be a bilateral process within the face motor cortices (Tate et al., 2014; Figure 1a).

In anomia, speech is partially preserved but nouns are difficult to retrieve. The epicenter of this function seems to be located in the posterior superior temporal gyrus and the inferior parietal lobule of the dominant hemisphere, corresponding to the "classical" Wernicke's area (Figure 1a,b). Two other regions are related to anomia. One lies more anteriorly within the inferior precentral gyrus, close to the lateral sulcus. The other lies in the junction between the posterior MFG and the precentral gyrus, which is also the junction between the dorsal and ventral premotor cortices (Tate et al., 2014; Figure 1a).

Semantic and phonological processes are widely distributed throughout the cortex in the dominant hemisphere. Semantics is associated with the junction of the posterior superior temporal gyrus and the supramarginal gyrus, pars triangularis, pars opercularis, and dorsal premotor cortex (Figure 1a,b). Phonology is associated with the middle superior temporal gyrus, the pars opercularis, and the junction of the dorsal and ventral premotor cortices (Figure 1a,b). The localization of semantic and phonological processes in the pars triangularis and the pars opercularis suggests that the classical Broca's area could actually be involved in higher-order tuning of language (Tate et al., 2014).

The AF (Figures 2a,b, 4c, 5b, 6b, and 7a,b) is associated with several language dysfunctions such as Broca's aphasia, alexia, agraphia,

conduction aphasia, reduced comprehension, anomia, dyslexia, Wernicke's aphasia, and transcortical sensory aphasia (Catani, Dell'Acqua, Bizzi, et al., 2012). Lesions in the uncinate (Figures 2a, 4b, and 7a) and inferior longitudinal (Figures 2a,b, 6b, and 7a) fasciculi are associated with semantic dementia. Injuries to the rostral portion of the corpus callosum and the anterior commissure are associated with right olfactory anomia. Cortical deafness for sounds or words is related to lesions in auditory thalamic projections (Catani, Dell'Acqua, Bizzi, et al., 2012).

Grammatical gender, an important aspect of syntactic processing, was analyzed using DES. Syntactic gender disturbances were observed by stimulating cortical regions in the dominant inferior frontal gyrus and the posterior MFG (Figures 1a; Vidorreta, Garcia, Moritz-Gasser, & Duffau, 2011). Axonal DES of the SLF can induce specific grammatical gender disorders without other dysfunctions (Duffau, 2015). On the basis of these findings, it was hypothesized that an independent subnetwork interacts with the sub-circuit involved in naming, an idea that supports the parallel hypothesis (Duffau, 2015). The anatomical and functional bases of syntactic processes are still unclear.

The verbal working memory system seems to involve the frontoparietal articulatory loop in the dorsal phonological stream, subserved by the lateral part of the SLF. This loop connects the dorsal part of the pars triangularis to the dorsal part of the supramarginal gyrus (Figure 1a,b). It has been associated with phonological working memory (Vigneau et al., 2006), allowing phonological information to be stored temporarily (Duffau, 2014). Therefore, this network is probably involved in repetition. This hypothesis is supported by DES-induced repetition disturbances in the posterior cortical terminations of the lateral part of the SLF (Martino et al., 2011; Quigg & Fountain, 1999; Quigg, Geldmacher, & Elias, 2006).

Intraoperative DES-elicited dysfunctions suggest a link between language and executive function. For instance, DES of the inferior frontal gyrus and the posterosuperior areas of the temporal lobe (Figure 1a,b), with subcortical stimulation of the SLF (Figures 2b, 4c, and 6b), produced involuntary language switching (Moritz-Gasser & Duffau, 2009a). These findings led to the speculation that the switching processes are subserved by a large-scale cortico-subcortical network controlled by the executive system, comprising the prefrontal cortex (Figure 1a), the anterior cingulum (Figure 4a), and the caudate nucleus (Figures 2a and 3a,b; Duffau, Gatignol, et al., 2009). Further evidence of a possible link between language and executive function is the perseveration of the head of the caudate nucleus induced by DES (Figure 3a; Robles et al., 2005).

3.3 | Language processing

A hodotopical model based on results from DES and functional studies has gradually replaced the localizationist viewpoint (Duffau, 2014, 2015). Hodotopy is the combination of cortical areas and connecting pathways forming interactive networks (Catani, 2007; De Benedictis & Duffau, 2011).

3.3.1 | Input

The first stage in the process of understanding language involves visual, auditory, or somatosensory input. Visual perception is the first stage of a language process elicited by visual input. The visual occipital cortex is connected to the posteroinferior temporal area (VOFA and VWFA) by the ILF fibers (Figures 2a,b, 6b, and 7a), and stimulation of this pathway triggers visual paraphasia (Catani et al., 2013; Gaillard et al., 2006; Mandonnet et al., 2009).

Subcortical DES of the occipitotemporal white matter tracts on the dominant hemisphere induced different symptoms in lower and upper fibers. In the same patients, stimulation of lower fibers induced alexia, while stimulating the upper fibers induced anomia (Duffau, 2015). Therefore, words and objects seem to be recognized by two distinct and parallel pathways originating from the visual occipital cortex.

Auditory input from the thalamus (Figure 3a,b) is processed in multiple locations such as the posterosuperior temporal areas and the supramarginal, angular, posterior middle temporal, superior, and middle occipital gyri (Figure 1a,b). These locations are interconnected by U-fibers (Duffau, 2015).

Somatosensory input information received from the thalamus is processed in the superior parietal lobule, the precuneus, the superior cingulate cortex, the SMA, the primary motor cortex, the prefrontal cortex, the MFG, and the orbitofrontal areas (Figures 1a,b and 4a), which are also interconnected by U-fibers (Duffau, 2015).

3.4 | Routes: Semantic versus phonological pathways

Visual and auditory language processes seem to branch into two main pathways, ventral semantic and dorsal phonological, which interact and work in parallel. In auditory language processing, the ventral stream could be involved in mapping sound to meaning, the dorsal stream in mapping sound to articulation (Hickok, 2012; Hickok & Poeppel, 2007; Saura et al., 2008). For visual language processing, this dual model was built on the basis of DES-induced separation between phonemic and semantic processes, demonstrating that these processes do not occur serially but in parallel (Duffau, 2014; Maldonado, Moritz-Gasser, De Champfleury, et al., 2011).

3.4.1 | Ventral semantic stream

The direct pathway of the ventral semantic stream is subserved by the IOFF (Figures 2a,b, 3a, 6b, and 7a). The IOFF connects the posterior occipital lobe and the VOFA to frontal areas such as the dorsolateral prefrontal cortex and the pars orbitalis (Figures 1a). DES of the IOFF resulted in semantic paraphasia (Duffau, 2015).

In addition to the direct pathway, there is an indirect pathway with a relay in the temporal pole. This indirect ventral stream is subserved by the anterior part of the ILF (Figures 2a,b, 6b, and 7a), which

connects the VOFA to the temporal pole. From the temporal pole, the information is relayed to the pars orbitalis by the UF (Figures 2a, 4b, and 7a; Duffau, Gatignol, et al., 2009). This sub-network can be bypassed to the direct pathway (IOFF) and functionally compensated (Duffau, 2009).

Another sub-network, the middle longitudinal fasciculus (MLF; Figures 6b and 7a), could be involved in the ventral semantic stream (Saura et al., 2008). This pathway connects the angular gyrus to the superior temporal gyrus (Figure 1a,b; Makris & Pandya, 2009). However, DES of this fasciculus has not elicited naming disorders, so its specific functional role remains unknown (De Witt Hamer, Moritz-Gasser, Gatignol, & Duffau, 2011).

3.4.2 | Dorsal phonological stream

The dorsal pathway is subserved by the SLF (Figures 2a,b, 4c, 5b, 6b, and 7a,b) and can be divided into two components. The deeper one is the AF (Figures 2a,b, 4c, 5b, 6b, and 7a,b), which runs from the posterior section of the middle and inferior temporal gyri, arches around the insula and moves toward the ventral premotor cortex and the pars opercularis (Figures 2a,b, and 5b).

In several studies, phonemic paraphasia was observed after DES of white matter around the superior and posterior parts of the superior insular sulcus (Bello et al., 2007; Benzagmout et al., 2007; Duffau, 2008; Duffau, Peggy Gatignol, et al., 2008; Maldonado, Moritz-Gasser, De Champfleury, et al., 2011; Maldonado, Moritz-Gasser, & Duffau, 2011). The VOFA, involved in both phonological and semantic processes, is the posterior cortical origin of the dorsal pathway. Stimulation of the AF induces conduction aphasia without semantic disorders. Conduction aphasia is a phonemic paraphasia combined with repetition disorders. These findings support the role of the AF in phonological processing (Duffau, 2015).

The more superficial component of the dorsal stream is subserved by the anterior part of the SLF (SLF III; Catani et al., 2005; Duffau, 2015). Anarthria was observed after DES of SLF III (Figures 2b, 4c, and 6b; Duffau, 2015). This bundle connects the junction of the posterior part of the superior temporal gyrus and the supramarginal gyrus to the ventral premotor cortex. Therefore, this system integrates somatosensory and auditory information with phonological-phonemic information to be translated into articulatory motor programs. This loop is also used during word repetition (Duffau, 2015).

3.5 | Output

Speech output is severely or entirely suppressed in anarthria. Recent studies based on cortical stimulation (Tate et al., 2014) have demonstrated that speech output has two crucial epicenters located in the precentral gyrus: the bilateral ventral premotor and the face motor cortices. The ventral premotor cortex lies in the inferior portion of the premotor gyrus just anterior to the primary motor cortex (Figure 1a)

and seems to be the most important region associated with speech output. It has similar patterns on both the dominant and nondominant sides in left-handed and ambidextrous patients.

On the other hand, speech output was rarely suppressed by stimulation of Broca's area (Tate et al., 2014). DES of the ventral part of the superior temporal gyrus and the posterior part of the supramarginal gyrus also elicited articulatory disorders (Benzagmout et al., 2007; Duffau, Capelle, Denvil, Sichez, et al., 2003; De Witt Hamer et al., 2011). This organization was similar in both hemispheres (Duffau, Leroy, et al., 2008).

Anarthria was induced by subcortical DES of white matter in the frontoparietal operculum and under the supramarginal gyrus (Figure 1a,b), anterolateral to the AF (Duffau, Capelle, Denvil, Gatignol, et al., 2003; Maldonado, Moritz-Gasser, De Champfleury, et al., 2011; Maldonado, Moritz-Gasser, & Duffau, 2011). SLF III, a pathway mentioned in the dorsal phonological stream, seems to be subserved by the operculo-opercular part of the SLF. DES of the direct insulo-opercular connections also induced anarthria (Benzagmout et al., 2007; Duffau, Moritz-Gasser, & Gatignol, 2009). These findings could relate the ventral premotor cortex to the insula, which is itself involved in the planning of vocal articulation (Dronkers, 1996; Duffau, Moritz-Gasser, & Gatignol, 2009).

3.6 | Final considerations

Currently, functional imaging technology and direct cortical stimulation are providing a new understanding of this complex network. Language comprises many specific functions located in different epicenters, which are correlated and interlinked by several pathways. These areas and connections can also be reorganized and relinked dynamically. In this study, we review the topographical anatomy and update information from functional studies that help understand the correlation between brain anatomy and language function.

Cortical and subcortical stimulation has challenged the classical theory of brain function and provided new insights into these complex networks. Broca's area, which comprises the pars opercularis and pars triangularis in the inferior frontal gyrus on the dominant side, was supposed to be essential for speech production. However, normal speech function has been preserved after resection of Broca's area (Benzagmout et al., 2007; Plaza et al., 2009).

Using current techniques, DES of the pars opercularis and pars triangularis has rarely elicited cessation of speech output, but rather phonological and semantic disorders. Therefore, Broca's area has been linked to modulation of higher-order aspects of language (Dronkers, 1996; Tate et al., 2014). On the other hand, speech output was prevented by stimulation of regions in the precentral gyrus such as the bilateral ventral premotor cortices and, less frequently, the face motor cortices (Tate et al., 2014).

Furthermore, anomia has been associated with other areas besides the classical Wernicke's area. This dysfunction resulted from stimulation of a more anterior region within the superior temporal gyrus, close to its junction with the inferior precentral gyrus. Anomia

resulted after a region close to the junction of the dorsal and ventral premotor cortices was stimulated (Tate et al., 2014).

Awake brain surgery with electrical mapping allows crucial areas to be recognized, improving the preservation of function and evaluation of the extent of resection. Understanding this complex and changing network is essential for achieving the challenging goal of continually providing better curative treatments while preserving quality of life.

Although intraoperative cortical stimulation helps to correlate function with anatomy, some issues interfere with the interpretation of findings. Patients subjected to cortical stimulation often have brain tumors that substantially modify brain anatomy. Slow-growing tumors allow brain functions affected by the tumoral mass to be restructured. This process is known as brain plasticity, which is the capacity of a noncrucial area to assume another area's function. Brain plasticity allows patients who have undergone surgery in a critical area to restore the same function in a different region.

4 | CONCLUSION

Cortical and subcortical stimulation, in addition to functional studies, has contributed to a better comprehension of language function. A hodotopical model is gradually replacing the classical localizationist theory. However, there are still numerous aspects of language anatomy to be revealed. A better understanding of the microsurgical anatomy of language can help us extend tumor resections while minimizing language deficits.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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