Seminars in
ULTRASOUND
CT and MRI

Imaging of Cortical and White Matter Language Processing

Andrew P. Klein, MD,* David S. Sabsevitz, PhD, ABPP,† John L. Ulmer, MD,* and Leighton P. Mark, MD*

Although investigations into the functional and anatomical organization of language within the human brain began centuries ago, it is recent advanced imaging techniques including functional magnetic resonance imaging and diffusion tensor imaging that have helped propel our understanding forward at an unprecedented rate. Important cortical brain regions and white matter tracts in language processing subsystems including semantic, phonological, and orthographic functions have been identified. An understanding of functional and dysfunctional language anatomy is critical for practicing radiologists. This knowledge can be applied to routine neuroimaging examinations as well as to more advanced examinations such as presurgical brain mapping.
Semin Ultrasound CT MRI 36:249-259

Introduction

The functional and anatomical relationships for language in the human brain have been widely studied using anatomical dissections, lesion localization studies, intraoperative stimulations, high-resolution imaging, and now functional imaging techniques including functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and magnetoencephalography. Unlike more elementary brain functional systems such as vision and sensorimotor, both of which have very similar anatomico-functional organization between human and nonhuman species, understanding the complex and uniquely human language system has been more elusive. From the beginning, models of language organization in the human brain have been proposed, accommodating data from the various methods of investigation. These language models are continuously modified as findings from cutting-edge research methods are added to our conceptualization. Although there is no doubt that our conceptualization of human language is incomplete and is subject to more modifications, it is important as radiologists to understand where we are. Radiologic practice is now more than ever integrated with the clinical neurosciences through instant access to the electronic health record. Being able to use anatomical, functional, and radiologic expertise in addition to clinical symptomatology and other nonimaging diagnostic parameters enables radiologists to provide accurate imaging interpretations and optimally influence patient management in scenarios ranging from routine stroke imaging to advanced applications such as presurgical brain mapping. The following is a discussion of important language cortical brain regions and white matter tracts in the context of functional language processing.

Functional Neuroanatomy of Language Processing

The scientific study of aphasia began in the early 19th century with Paul Broca's description of a patient who lost the ability to express but not comprehend speech following damage to the posterior portion of the inferior frontal lobe. Shortly after Broca's discovery, Carl Wernicke described a different form of aphasia in which language comprehension was disrupted but not speech expression following damage to the posterior superior temporal gyrus (STG). Based on these clinical-anatomical observations, Wernicke proposed the first brain behavioral model in which language was localized to two main regions: (1) an area in the left inferior frontal lobe (now known as Broca's area) that contains the motor memories responsible for speech production and (2) an area in the left posterior temporal lobe (now known as Wernicke's area) that contains

*Department of Radiology, Medical College of Wisconsin, Milwaukee, WI.
†Department of Neurology, Medical College of Wisconsin, Milwaukee, WI.
Address reprint requests to Andrew P. Klein, MD, Department of Radiology, Medical College of Wisconsin, 9200 West Wisconsin Ave., Milwaukee, WI 53226. E-mail: AKlein@mcw.edu

http://dx.doi.org/10.1053/j.sult.2015.05.011
0887-2171/

the auditory images of words responsible for speech perception. These two regions communicate with each other through a bundle of fibers later identified as the arcuate fasciculus (AF). This model was the first to associate specific language deficits with discrete anatomical regions.

Although the basic principles and predictions of Wernicke's classical localization model still hold true, mainly that the inferior frontal lobe plays an important role in speech production and the posterior temporal region is important for speech comprehension, the advent of modern structural and functional imaging has expanded our knowledge of the neuroanatomical underpinnings and functional components of language processing. It is now accepted that language involves a number of conceptually distinct but interacting linguistic subsystems located in a widely distributed network, including several regions outside the classic language areas. What follows is a brief review of the organization and neuroanatomy of language processing.

Orthographic Processing

Orthography refers to information concerning written letter combinations and is important for reading and writing. Clinical and functional neuroimaging studies have identified an area in the left ventral occipitotemporal cortex, now referred to as the visual word form area (VWFA), as a putative region for orthographic processing (Fig. 1, area colored in light blue). This area is reliably activated during reading, and the focus of this activation is often within a few millimeters across studies and across languages. It has also been shown that neurons in this region become tuned to processing orthographic content, as this region shows greater activation in literate than in illiterate individuals.[1] This region activates more strongly to words or wordlike nonwords than to consonant strings or false font characters,[2-5] and the activation in this area is not modulated by letter case or other basic visual characteristics of the stimuli.[6,7] It has also been demonstrated that activation in the VWFA is specific to written stimuli when compared with spoken stimuli, independent of the stimuli's semantic content.[7] These findings have led to the belief that the VWFA extracts an abstract representation of the letter identity. Additionally, in an fMRI study by Binder et al,[8] the VWFA demonstrated a unique graded response to the orthographic regularity or letter sequence probability of meaningless letter strings. The more the letter strings approximated English orthography, the greater the activation. This response was specific to the VWFA. Lesion studies further support the role of this region in orthographic processing. Damage to the VWFA results in a pure alexia, a condition where language functions are normal (including speaking and comprehension), and patients can often identify single letters without much difficulty but reading letter strings is extremely slow and effortful and limited to a letter-by-letter reading strategy.

Phonological Processing

Phonology refers to the articulatory and perceptual characteristics of speech sounds and is important for speech perception and the selection of speech sounds during production of spoken speech. There is evidence from lesion and functional imaging studies suggesting the existence of separable input and output phonological pathways. Listening to speech sounds (eg, syllables, words, pseudowords, and reversed speech) when compared with silence activates large areas in the STG

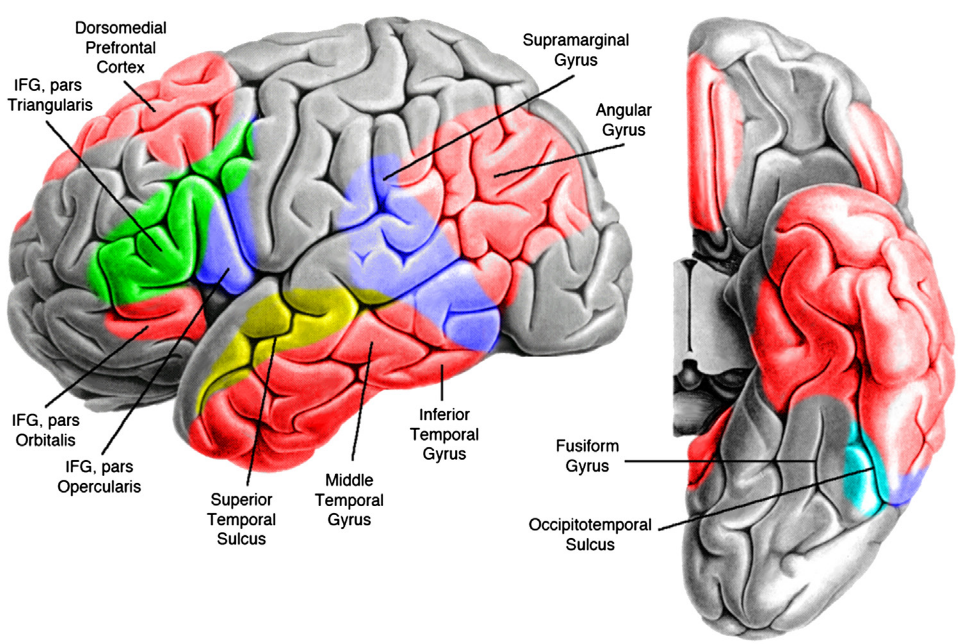

Figure 1 Yellow = phoneme and auditory word form perception areas, red = semantic storage and retrieval systems, blue = phonological access and phonological output systems, light blue = visual word form perception area, green = general verbal retrieval, selection, and working memory functions. (Reproduced with permission from Binder JR: *Functional Neuroradiology: Principles and Clinical Applications*, 2011.) (Color version of figure is available online.)

bilaterally. Within the STG, symmetric activation is seen in Heschl's gyrus and the dorsal areas surrounding Heschl's gyrus. However, this activation is not specific to speech sounds, as it is also activated by nonspeech sounds (eg, frequency-modulated tones), suggesting that low-level auditory processing and not phoneme-level processing occurs in these areas.[9] However, preferential activation has been reported to be more anterior and ventral in the superior temporal sulcus (left greater than right) in response to speech sounds when compared with nonspeech sounds that attempt to control for the acoustic complexity of the stimuli[9-11] (Fig. 1, area colored in yellow). Activation in this area is also seen when spectrally rotated speech that preserves the overall spectrotemporal complexity of the stimuli but renders phonemes unintelligible is used as a control[12,13] and when speechlike sounds that have no phoneme identity are used as control stimuli.[14] Bilateral lesions to the STG can result in pure word deafness where there is a marked impairment in speech sound recognition, but basic hearing, speech production, and reading and writing are preserved. Patients with this condition have impaired phoneme discrimination but relatively normal auditory acuity. These findings suggest that this region may be involved in processing input phonemes, in particular, mapping acoustic waveforms onto abstract speech sound codes (auditory word form processing). The selection and processing of output phonemes has been linked to the posterior STG (Fig. 1, area colored in blue). Lesions to the posterior STG can produce selective impairments in selecting and ordering phonemes during speech production, resulting in frequent phonemic paraphasic errors, while leaving phoneme perception and auditory comprehension intact (ie, features seen in conduction aphasia). Electrical stimulation of the posterior STG has been shown to produce phoneme sequencing and selection errors,[15] and functional imaging studies have shown activation in this region in response to tasks requiring word production and phoneme retrieval (eg, making decisions about pronounceable vs unpronounceable consonant strings, silent-word generation, and picture naming; see Ref. 16 for a meta-analysis of word production experiments). The inferior frontal lobe (in particular pars opercularis) and the supramarginal gyrus are also often activated during tasks requiring maintenance and manipulation of phonological information and consequently have been implicated in phonological buffering and segmentation.

Semantic Processing

Semantics refers to information about word meanings and other declarative and factual knowledge acquired through experience. Storage and retrieval of semantic knowledge is thought to be widely distributed throughout the dominant and to a lesser extent, in the nondominant hemisphere (Fig. 1, areas colored in red and green). A meta-analysis of 120 functional neuroimaging studies focusing on semantic processing revealed a left lateralized network consisting of the posterior inferior parietal lobe (angular gyrus), lateral and ventral temporal cortex, posterior cingulate cortex, and areas in the frontal cortex including the dorsomedial and ventromedial prefrontal and inferior frontal cortices.[17] The angular gyrus was the most frequently reported site of activation in this meta-analysis. Although the precise contribution of the angular gyrus to semantic processing is unclear, its heteromodal nature suggests that it may serve as a convergence zone for bringing together and integrating information across sensory modalities for semantic processing. The lateral and ventral temporal cortex, including the middle temporal lobe and portions of the inferior temporal lobe and fusiform gyrus, has also been implicated in semantic processing and is frequently activated in response to a wide range of semantic tasks.[17] Semantic dementia, a neurodegenerative condition characterized by progressive loss of semantic- and word-level knowledge with relative sparing of phonological processing during the early stages of the disease, has been associated with anterior temporal atrophy.[18,19] Structural lesions to the temporal lobe areas can also cause impairments in semantic processing, and in some cases, the impairments can be highly circumscribed and category specific.[20,21] The presence of category-specific deficits suggests possible category- or modality-specific semantic representations in the temporal lobe. The dorsal and medial frontal lobe is also frequently activated in functional neuroimaging studies during semantic tasks. Lesions to this region can cause a transcortical motor aphasia where speech production is slow and effortful, with greater impairment in accessing semantic knowledge in the absence of constraining cues (fluency tasks often impaired while confrontation naming grossly preserved), perhaps suggesting that this region may be involved in initiating and directing semantic information retrieval. Lastly, activation is commonly reported in the anterior portion of the inferior frontal gyrus (pars orbitalis) in response to semantic tasks. However, its contribution to semantics is unclear, as it has been implicated in phonological, working memory, and syntactical processing as well.

Syntactical Processing

Syntax refers to the rules and principles that govern sentence-level word ordering that connote relationships between words. For example, the phrase "the boy's mother" has a different meaning than "the mother's boy" because of differences in word ordering. The inferior frontal operculum and anterior temporal lobe have both been identified as possible regions involved in sentence-level or syntactical processing. Damage to the inferior frontal operculum, otherwise known as Broca's area, results in nonfluent or effortful speech with auditory comprehension largely preserved. On closer examination, these patients often reveal deficits in comprehension of complex syntax. Additionally, patients with Broca's aphasia often produce agrammatical or telegraphic speech whereby function words are omitted (eg, get milk store). A number of functional imaging studies have shown activation in this region during processing of syntactically complex sentences when compared with less complex sentences[22-24] as well as in studies contrasting syntactically correct vs incorrect sentences.[25] The lateral portion of the anterior temporal lobe is also activated in functional imaging studies examining syntactical processing. For example, several studies showed activation in the anterior temporal lobe in response to paradigms that compared listening to sentences vs random words lacking coherent sentence structure.[26-28] Humphries et al[29] conducted an fMRI study in which word order and combinatorial word meaning were independently manipulated during an auditory comprehension task to better isolate syntactic vs semantic-level processing. This showed greater activation in the left anterior superior temporal sulcus for sentences when compared with random words, with no significant difference in this area in response to semantically congruent and semantically random stimuli. These findings suggest that this region was not simply processing the increased semantic information presented in the sentences, but rather the presence of syntactical structure.

Language White Matter

Recently, there have been major advances in our understanding of white matter organization, thanks to innovations in anatomical dissection, noninvasive neuroimaging, and neurosurgical techniques. Application of autoradiographic tract-tracing techniques using radioactive isotopes in nonhuman primates has yielded important details of major white matter tracts, including trajectories, origins, and terminations.[30] Although there are obvious differences between humans and nonhuman primates in language ability and higher cognitive function, anatomical organization of white matter between the two groups is remarkably similar. Language white matter differences between the two groups have been described and discussed.

On the imaging front, DTI with fiber tracking has had a profound effect on our understanding of white matter.[31-35] No longer are we limited to thinking about lobar or regional white matter on MRI. Color-coded fractional anisotropy (FA) maps reveal individual association, projection, and commissural white tracts,[36] some with known and some with incompletely understood functions. Neuroscience in general and neuroradiology in particular are in the midst of an important discovery phase, as we build an understanding of white matter functional and dysfunctional anatomy.[37,38] DTI fiber tracking has been used in concert with fMRI to apply and establish language models,[39] incorporating findings of active cortical regions and visualized white matter tracts subserving these areas, based on white matter origins and terminations. However, current limitations in the DTI technique, including spatial resolution and intravoxel analysis of crossing fibers, remain a barrier in the complete characterization of white matter tracts.[40,41] Interestingly, much of the DTI fiber-tracking work on cortical origins and terminations of white matter tracts in the human uses *a priori* hypotheses derived from the nonhuman primate autoradiographic data, if not the data as the de facto gold standard. However, caution must be used in categorical application of the nonhuman primate white matter data, especially as they pertain to the language system.

Although electrical cortical stimulation mapping has provided insight into, and verification of, eloquent cortex,[42,43] direct electrical white matter stimulation mapping, a highly specialized technique, has provided a unique opportunity to investigate the white matter functional anatomy.[44-49] During an awake procedure (usually brain tumor resections), the patient performs a specific cognitive task while the neurosurgeon stimulates a specific white matter tract. If the stimulation is accompanied by impaired function, that tract is assumed to play a role in that function. A major advantage of this technique is that it produces a transient virtual lesion by inhibiting a functional network as opposed to permanent lesions found on neuroimaging. Limitations for this technique are invasiveness, possibility of distorted anatomical relationships from the pathologic process, and operator dependence. Additionally, agreement between intraoperative tract stimulation and tract identification on preoperative DTI fiber tracking is not perfect.[50]

Presently, there is controversy and debate regarding the anatomical connections and functions of most of the putative language white matter tracts. Discrepant findings and proposed concepts derived from the various techniques of blunt dissection of human white matter, autoradiographic tract tracing in the nonhuman primate, in vivo human DTI fiber tracking, and intraoperative electrical stimulation result in a complex and uncertain language white matter framework. Much of this is beyond the scope of this article. An excellent review of these controversies and the evolving historical understanding of the putative language white matter tracts is available.[51] The following discussion of language white matter is designed as a practical and useful guide for interpreting radiologists, highlighting anatomical and functional relationships of these tracts. Color-coded FA DTI maps are presented for anatomical localization (Fig. 2).

Dual-Stream Language Processing

Many human language models have been proposed, and even more modifications to these models have been proposed. If one thing is clear, the human brain is complex. If a language model is to stand the test of time, it has to be consistent with lesion localization studies, clinical aphasias, as well as intraoperative evaluations. Much like the dual-stream model of visual information processing with a dorsal component dedicated to spatial processing (the "where" stream) and a ventral component dedicated to object recognition (the "what" stream), most current models for auditory language processing are based on a dual-stream model.[52-57] In this model, a dorsal phonological stream maps sound to articulation and a ventral semantic stream maps sound to meaning. The superior longitudinal fasciculus (SLF) is widely regarded as the most important, if not the entire dorsal phonological stream. Much more debate and uncertainty surrounds the ventral semantic stream. Various white matter tracts have been implicated in the ventral stream including the extreme capsule, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), middle longitudinal fasciculus (MdLF), and uncinate fasciculus (UF). Furthermore, direct and indirect pathways for the ventral language stream have recently been proposed with the direct pathway represented by the IFOF and the indirect pathway represented by the anterior part of the ILF and the UF.[58,59]

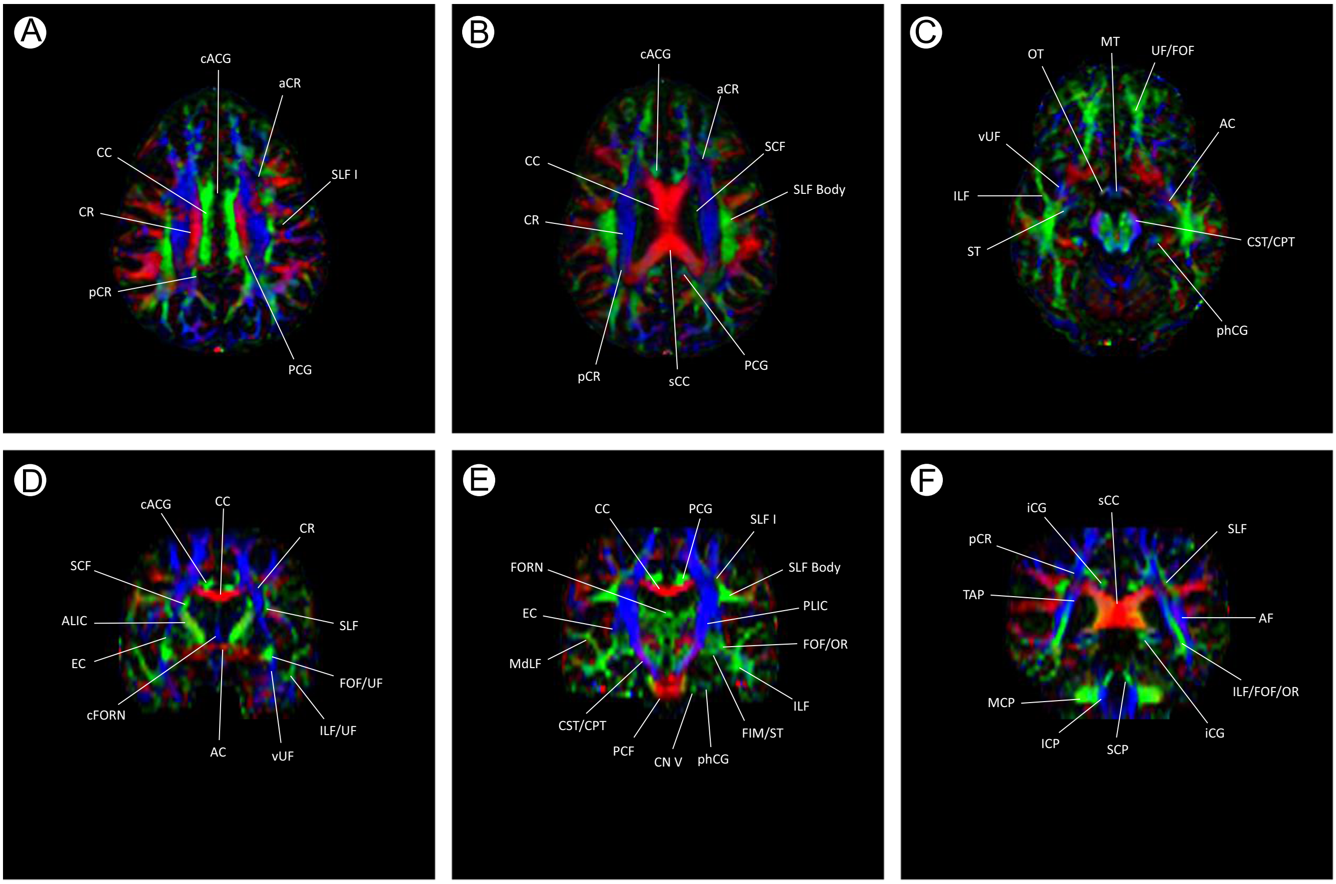

Figure 2 (A-C) Axial color-coded FA maps from superior to inferior and (D-F) coronal color-coded FA maps from anterior to posterior. AC, anterior commissure; aCR, anterior corona radiata; ALIC, anterior limb of internal capsule; cACG, caudal anterior cingulum; CC, corpus callosum; cFORN, forniceal columns; CN V, cranial nerve V; CR, corona radiata; CST/CPT, corticospinal tract and corticopontine tract; EC, external capsule; FIM, fimbria; FORN, fornix; iCG, isthmus of cingulum; MCP, middle cerebellar peduncle; MT, mammillothalamic tract; OR, optic radiations; OT, optic tract; PCF, pontocerebellar fibers; PCG, posterior cingulum; pCR, posterior corona radiata; phCG, parahippocampal cingulum; PLIC, posterior limb of internal capsule; sCC, splenium of corpus callosum; SCF, subcallosal fasciculus; SCP, superior cerebellar peduncle; ST, stria terminalis; TAP, tapetum; vUF, vertical fibers of uncinate fasciculus.

Dorsal Pathway

The SLF is the largest of the paired major association tracts with the cerebrum. Each SLF is located lateral to the corona radiata and connects the hemisphere's frontal lobe cortical regions with temporal and parietal cortical regions. It connects prefrontal and premotor areas with posterior language areas. Recently, a number of conflicting descriptions of the SLF have emerged, each containing a different method of parcellation.[30,39,60-62] The dominant theory derived from nonhuman primate dissections and verified by DTI fiber-tracking studies on humans asserts that the SLF has 4 subcomponents: SLF I, SLF II, SLF III, and SLF IV (AF)[30,62,63] (Fig. 3). It should be noted that although early anatomists considered the SLF and AF to be synonymous, recent data from these nonhuman primate dissections and fiber-tracking studies have shown that the AF is merely a subcomponent, namely SLF IV. Therefore, results from lesion localization studies throughout the 19th century and most of the 20th century could be confusing if this is not taken into consideration. Additionally, comparison of old and new lesion localization study results on the SLF and the AF should be done with caution.

SLF I is located in the white matter of the superior parietal and superior frontal lobes and extends to the dorsal premotor and dorsolateral prefrontal regions (Fig. 3A). On color-coded FA maps, SLF I is green and located more superiorly than the other subcomponents, occupying a pericallosal and supracallosal position (Fig. 2A and E). The superior parietal lobule encodes and integrates information about the location of body parts in space, whereas the supplementary motor area and premotor areas are important in planning, initiation, and execution of higher motor behavior. Based on the cortical connections, injury to SLF I is expected to cause executive dysfunction and perseveration errors.

SLF II occupies the central core of the white matter above the insula. It extends from the angular gyrus to the caudal-lateral prefrontal and premotor regions (Fig. 3B). SLF II is also green on color-coded FA maps, with fibers running in the anteroposterior and posteroanterior directions. Together with SLF III and the horizontal portion of SLF IV, SLF II forms the

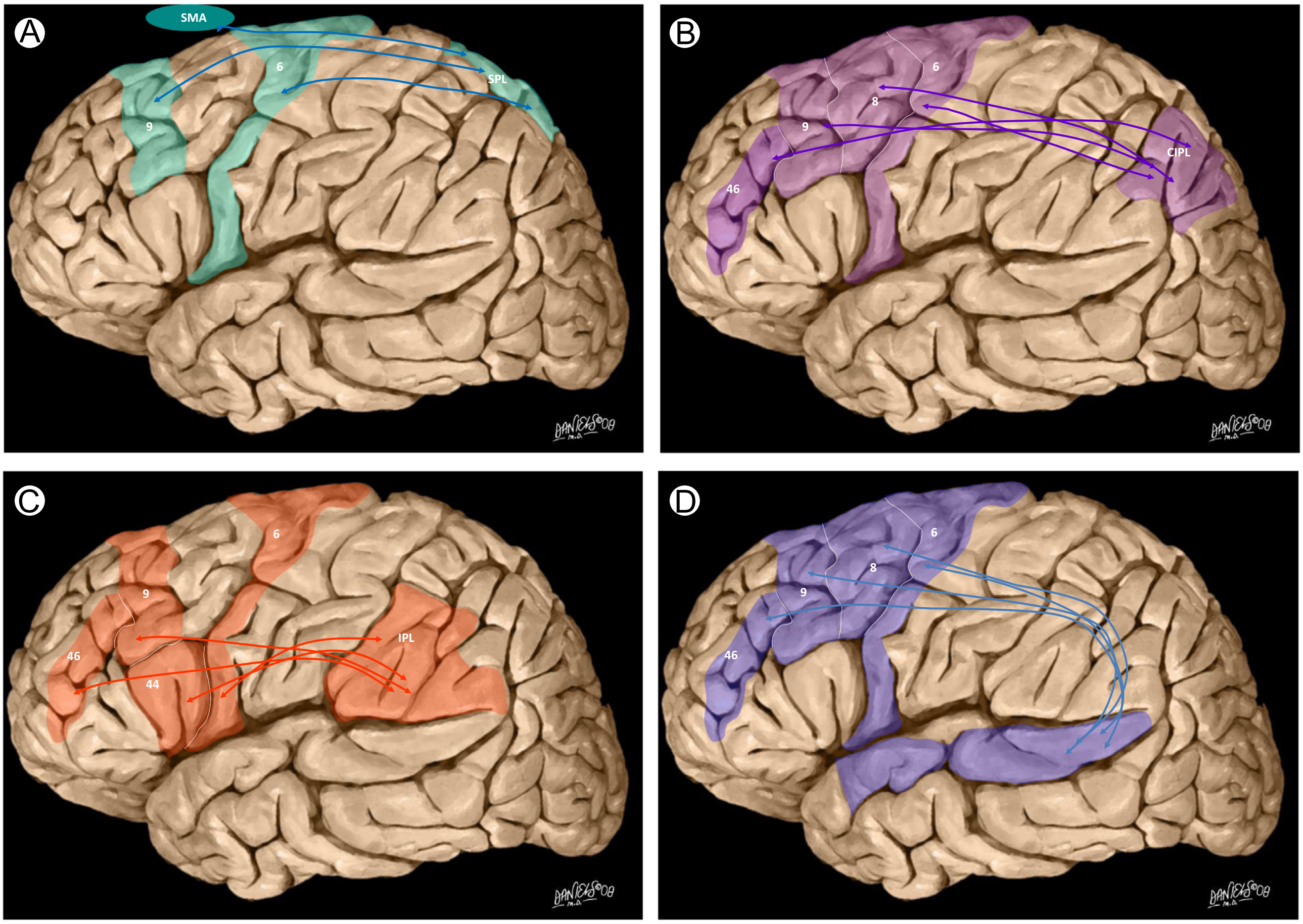

Figure 3 Illustrations indicating Brodmann area connections for the subcomponents of the superior longitudinal fasciculus (SLF) based on nonhuman primate dissections[30] and DTI fiber-tracking data.[63] A = SLF I, B = SLF II, C = SLF III, D = SLF IV (arcuate fasciculus). IPL, inferior parietal lobule; SMA, supplementary motor area; SPL, superior parietal lobule; CIPL, caudal inferior parietal lobule. (Illustrated brain modified with permission from Henri M. Duvernoy: *The Human Brain Surface, Blood Supply, and Three-Dimensional Sectional Anatomy*). (Color version of figure is available online.)

SLF body (Fig. 2B and E). The angular gyrus is important in visuospatial function, and injury to this subcomponent would be expected to cause deficits of spatial attention and spatial working memory.

SLF III is the most laterally positioned of the subcomponents, situated in the parietal and frontal opercula, extending from the supramarginal gyrus to the ventral premotor, Broca's and prefrontal areas (Fig. 3C). Green SLF III fibers on DTI are located lateral to horizontal SLF II and SLF IV fibers. The inferior parietal lobule provides the ventral premotor and Broca's area with complex somatosensory information, important in the articulatory component of language. Based on the cortical connections, injury to SLF III would be expected to cause ideomotor apraxia and orofacial apraxia.

SLF IV, the AF, extends from the posterior part of the STG, arches around the posterior end of the sylvian fissure, and projects to the lateral prefrontal and premotor cortices along with SLF II fibers (Fig. 3D). On color-coded FA maps, this subcomponent has both anterior horizontal (green) and posterior vertical (blue) portions (Fig. 2B and D-F). Auditory spatial information from the superior temporal lobe is conveyed to the caudal dorsolateral prefrontal cortex. Injury to SLF IV would be expected to cause impaired auditory discrimination.

Segmentation of the SLF into these subcomponents reveals some interesting findings. First, according to these studies, the AF may not actually connect to the pars opercularis (Broca's area) as commonly believed. In fact, it is SLF III that is thought to be important in the articulatory component of language that connects to pars opercularis. Perhaps SLF III is a major language pathway. The AF does, however, have posterior connections to Wernicke's area, Brodmann area 22. Maybe all of this is less surprising given that the terms SLF and AF were used interchangeably for so many years. What has been described in previous studies as connecting the Broca's to Wernicke's areas is the SLF as a whole, not the AF (SLF IV).

Another interesting result of the SLF segmentation is the difference between projected neurologic impairments for each subcomponent based on cortical connections and the actual deficits in the literature from lesion localization studies. Although conduction aphasia is the classic language deficit associated with left SLF injury,[64,65] observed language deficits for the SLF have also included primary progressive aphasia,[66] impaired repetition and impaired comprehension,[67] anomia,[44] and speech arrest.[68] These are far different from the proposed deficits as discussed earlier. The exact reason for this is unclear. A possible explanation is that the occurrence of isolated SLF subcomponent injury is likely rare, and recognizing it as such would be difficult. DTI is not a routine brain MRI sequence. Compensatory and network redundancy factors could potentially confound this as well by masking or mitigating the deficit. Another plausible explanation for the differences between proposed and observed deficits may be the relative difficulty in recognizing or testing for the proposed deficits. Unlike conduction aphasia, which has such a distinctive and conspicuous presentation (see the document from *Snow White and the Seven Dwarfs*), diagnoses of perseveration errors, compromised spatial working memory, impaired auditory discrimination, etc are more difficult. Additionally, statistically speaking, isolated presentation of one of these proposed deficits in the real world would likely be the exception rather than the rule.

So how should this information about the SLF be used clinically? Well, regardless of the debate surrounding the exact cortical connections, tract parcellation, and discrepant functions or dysfunctions, it is clear that there is an association between SLF damage and language impairment based on multiple reports of actual patients throughout the literature. The weight of the evidence from these lesion localization studies, as well as combined fMRI and DTI and intraoperative electrical stimulation studies, suggests that the dominant SLF plays a crucial role in the dorsal phonological system, and injury to this major association tract puts the patient at risk for significant language impairment. In neurosurgical procedures, neuroradiology practice, and otherwise, the dominant SLF is treated as a critical and eloquent structure.

Case Example

A 72-year-old woman with a 2-week history of transient word-finding difficulties, paraphasic errors, confusion, and right-sided face weakness presents to her neurologist. A brain MRI was performed demonstrating a large rim-enhancing cystic mass centered within the left anterior subcentral gyrus region (Fig. 4A and B).

Presurgical fMRI was performed, demonstrating left hemispheric dominance for language (not shown). DTI demonstrates a ball-in-glove configuration of the mass with the SLF and corticobulbar motor fibers. The horizontal fibers of the SLF are displaced by the mass and have asymmetrically decreased FA (yellow arrows, Fig. 4C-E). These horizontal fibers of the SLF have immediate proximity to the medial and the superior margins of the lesion. Transversely oriented corticobulbar fibers (red fiber tracts labeled with dashed white arrow, Fig. 4F), which are known to extend through the horizontal SLF (green fiber tracts labeled with solid white arrows, Fig. 4F), are also expected to have proximity to the posterosuperior and superior margins of the lesion.

The neurosurgeon performed an awake craniotomy and resection with intraoperative mapping and functional dissection testing. Ultrasonic stimulation along the medial and superomedial borders induced transient speech disruption, presumably related to SLF stimulation. Additionally, stimulation along the posterosuperior border induced right body corticobulbar dysfunction. Following surgical resection of the cystic lesion, precontrast (Fig. 4G) and postcontrast (Fig. 4H) images indicated a small amount of residual enhancement along the medial and posterior margins of the resection cavity (green arrows). The neurosurgeon opted to be nonaggressive along these borders to avoid both language and corticobulbar deficits. The patient did well postoperatively. The final diagnosis was Glioblastoma.

Ventral Pathway

The IFOF is purported to be a long association tract connecting the ventrolateral and dorsolateral prefrontal cortices with occipital, parietal, and posterior temporal cortices, verified by numerous DTI studies.[61,63,69,70] The IFOF passes through the anterior floor of the external capsule, extending along the superior margin of the UF within frontal region.[71,72] Recently, human anatomical dissections have revealed 2 subcomponents for the IFOF. The superficial and dorsal subcomponent connects the frontal lobe with the superior parietal lobe and the posterior portion of the superior and middle occipital gyri. The deep and ventral subcomponent connects the frontal lobe with the posterior portion of the inferior occipital gyrus and the posterior temporobasal area.[73] On color-coded DTI, the IFOF appears green and its posterior extent is inseparable from the ILF and optic radiations (Fig. 2C-F). It is noteworthy that nonhuman primate studies have not demonstrated an equivalent pathway and others have argued that the IFOF and ILF are not distinct, but actually part of the same tract.[30] Given its occipital connections, the IFOF is thought to play a role in visual spatial processing (dorsal visual processing stream) and visual recognition (ventral visual processing stream).[74,75] Additionally, intraoperative electrical stimulation of the IFOF in humans has reportedly caused semantic paraphasias (word substitution with related meaning to the intended word, eg, car for van),[45] possibly implicating this tract as an essential component of the ventral semantic language stream.

The ILF is an association tract connecting the temporal lobe with the occipital lobe. White matter fibers of the superior, middle, and inferior temporal gyri and the fusiform gyrus project to the lingual, cuneus, and lateral occipital lobes. Fibers also connect occipital areas with the hippocampus and the uncus, and parahippocampal gyri.[71,76] On color-coded FA maps, the ILF is green and best identified as a distinct tract within the temporal lobe. At its posterior extent, it is inseparable from the IFOF and optic radiations (Fig. 2C-F). It is thought to be involved in visual associative memory, analysis of visual motion, visual spatial analysis, and attention.[37,38] Lesions disrupting the ILF pathway would interrupt the transfer of information among visual, limbic, and memory areas, causing visual agnosias (disorder of recognition), visual memory errors, and visual hypoemotionality.[77,78] Additionally, it may play a cooperative role in the ventral semantic language stream.[79,80]

The UF is an association tract that connects the anterior and medial temporal lobe (including amygdala) with the inferior frontal lobe.[72] On color-coded FA maps, the UF has both green

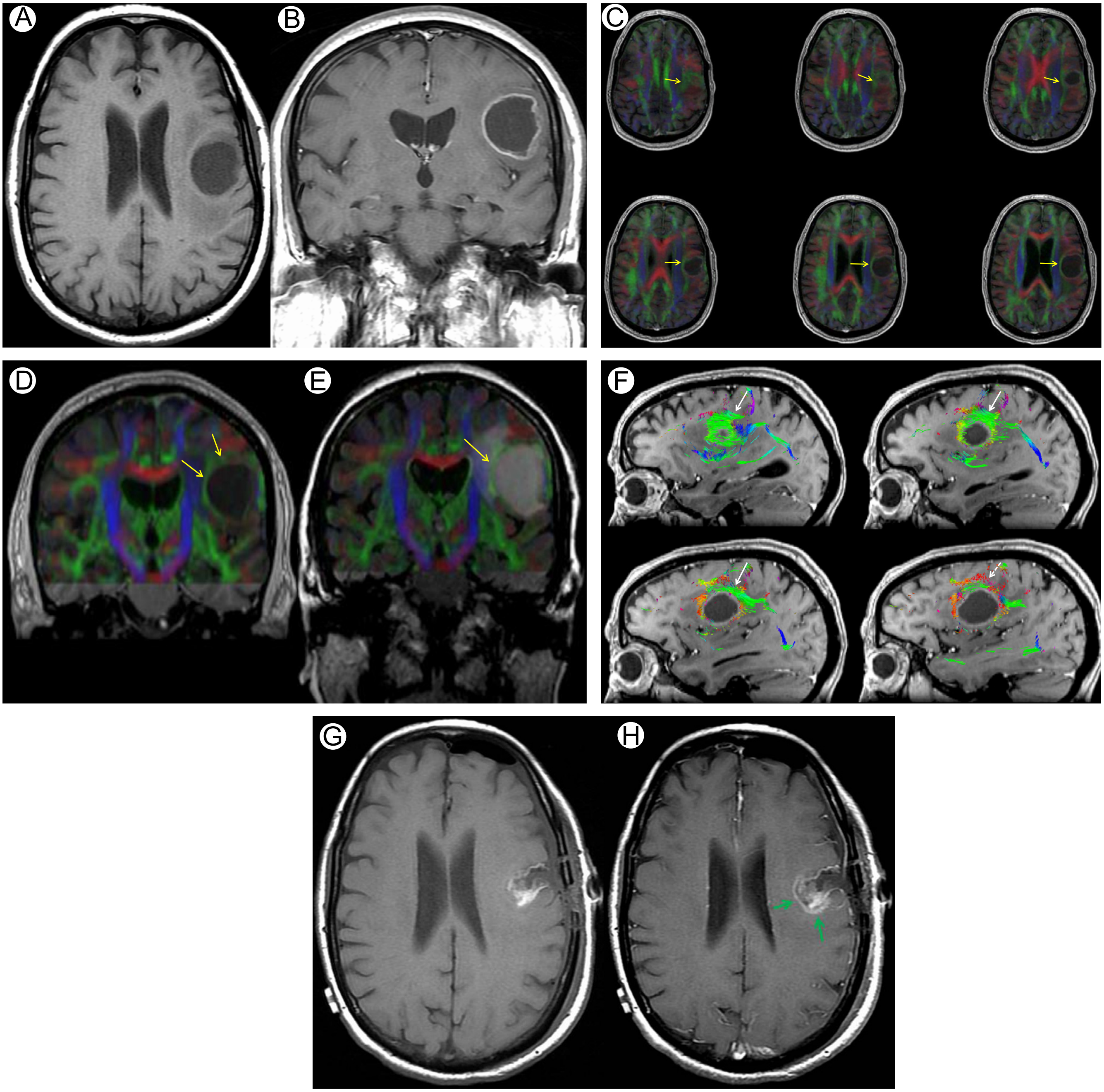

Figure 4 Axial precontrast (A) and coronal postcontrast (B) T1-weighted images, sequential axial DTI color-coded FA maps from superior to inferior superimposed on postcontrast SPGR images (C), coronal DTI superimposed on postcontrast SPGR (D) and FLAIR (E) images, sagittal postcontrast SPGR images presented medial to lateral with superimposed deterministic fiber tracking (F), and axial precontrast (G) and postcontrast (H) T1-weighted images. FLAIR, fluid attenuation inversion recovery; SPGR, spoiled gradient recalled echo acquisition in steady state. (Color version of figure is available online.)

horizontal and blue vertical components (Fig. 2C and D). Although it runs for a short length along the inferior margin of IFOF, these green tracts are difficult to differentiate on DTI. Because of its temporal connections, proposed functions include auditory working memory, sound recognition, and attachment of emotional significance to auditory stimuli. Specifically, the right UF engages multimodal imagery necessary for retrieval of autobiographical or event memories, whereas the left UF is important for storage of and access to remote semantic and lexical memories.[81,82] Consequently, injury to the right UF may result in impaired memory of episodic or personal experiences and injury to the left UF may result in impaired memory of learned concepts and facts.[81,82] The UF has been proposed to work cooperatively with the ILF, contributing to the indirect pathway for the ventral semantic stream.[58,59]

The extreme capsule is a relatively small and thin white matter tract located between the claustrum and the insula, running parallel to and often confused with the external capsule. Although identified in nonhuman primate studies, it is often absent or not identified in DTI studies, possibly owing to limitations in spatial resolution. A combined DTI and fMRI study suggested that the extreme capsule connects cortical areas active during auditory comprehension of meaningful stimuli as opposed to nonmeaningful stimuli.[79,83] However, some have questioned whether this was misrepresented, and whether this was in fact the external capsule.[84] A role in semantic language processing for the extreme capsule is possible, though controversial. A DTI study evaluating FA has recently suggested a role in phonological working memory as well.[85]

Another association pathway that has been described in nonhuman primates is the MdLF.[30] Its existence is absent in many human DTI studies. However, a recent DTI study does identify this tract as it runs within the STG from the temporal pole, extending caudally in the upper part of the sagittal stratum and the posterior corona radiata, reaching the angular gyrus.[86] It is positioned lateral and superior to the IFOF and perhaps previously assumed to be a part of the IFOF on color-coded FA maps (Fig. 2E). Given the functional importance of angular gyrus, the MdLF may have a role in spatial attention, attention processing, and episodic memory in the nondominant hemisphere[87] and semantic language in the dominant hemisphere.[46] However, a combined DTI and fMRI study suggested MdLF roles in both dorsal and ventral language processing routes.[79] To date, there have been few studies regarding the MLF. In light of its recent identification in humans, investigations into its functional significance would be forthcoming.

Conclusion

Although human language models continue to evolve based on evidence from cutting-edge research techniques such as fMRI and DTI, an understanding of important cortical brain regions and major white matter tracts for linguistic processing would empower radiologists in everyday clinical practice. Our neuroscience clinical partners from neurology, neurosurgery, and neuropsychology are closer to us than ever before. Through instant access to the electronic health record, the radiology domain increasingly overlaps with these other specialties. Using clinical examination and nonimaging diagnostic data with a firm grasp of the anatomico-functional correlation in language processing makes imaging more powerful than ever.

References

1. Dehaene S, Pegado F, Braga LW, et al: How learning to read changes the cortical networks for vision and language. Science 330(6009):1359-1364, 2010
2. Cohen L, Lehericy S, Chochon F, et al: Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. Brain 125(Pt 5):1054-1069, 2002
3. Dehaene S, Naccache L, Cohen L, et al: Cerebral mechanisms of word masking and unconscious repetition priming. Nat Neurosci 4 (7):752-758, 2001
4. Polk TA, Farah MJ: Functional MRI evidence for an abstract, not perceptual, word-form area. J Exp Psychol Gen 131(1):65-72, 2002
5. Tarkiainen A, Helenius P, Hansen PC, et al: Dynamics of letter string perception in the human occipitotemporal cortex. Brain 122(Pt 11):2119-2132, 1999
6. Cohen L, Dehaene S, Naccache L, et al: The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 123(Pt 2):291-307, 2000
7. Dehaene S, Clec' HG, Poline JB, et al: The visual word form area: A prelexical representation of visual words in the fusiform gyrus. Neuroreport 13(3):321-325, 2002
8. Binder JR, Medlar DA, Westbury CF, et al: Tuning of the human left fusiform gyrus to sublexical orthographic structure. Neuroimage 33(2): 739-748, 2006
9. Binder JR, Frost JA, Hammeke TA, et al: Human temporal lobe activation by speech and nonspeech sounds. Cereb Cortex 10(5):512-528, 2000
10. Jancke L, Wustenberg T, Scheich H, et al: Phonetic perception and the temporal cortex. Neuroimage 15(4):733-746, 2002
11. Zatorre RJ, Evans AC, Meyer E, et al: Lateralization of phonetic and pitch discrimination in speech processing. Science 256(5058):846-849, 1992
12. Scott SK, Blank CC, Rosen S, et al: Identification of a pathway for intelligible speech in the left temporal lobe. Brain 123(Pt 12):2400-2406, 2000
13. Friederici AD, Kotz SA, Scott SK, et al: Disentangling syntax and intelligibility in auditory language comprehension. Hum Brain Mapp 31(3):448-457, 2010
14. Liebenthal E, Binder JR, Spitzer SM, et al: Neural substrates of phonemic perception. Cereb Cortex 15(10):1621-1631, 2005
15. Quigg M, Fountain NB: Conduction aphasia elicited by stimulation of the left posterior superior temporal gyrus. J Neurol Neurosurg Psychiatry 66 (3):393-396, 1999
16. Indefrey P, Kleinschmidt A, Merboldt KD, et al: Equivalent responses to lexical and nonlexical visual stimuli in occipital cortex: A functional magnetic resonance imaging study. Neuroimage 5(1):78-81, 1997
17. Binder JR, Desai RH, Graves WW, et al: Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 19(12):2767-2796, 2009
18. Chan D, Fox NC, Crum WR, et al: Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol 49(4):433-442, 2001
19. Mummery CJ, Patterson K, Price CJ, et al: A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. Ann Neurol 47(1):36-45, 2000
20. Hillis AE, Caramazza A: Category-specific naming and comprehension impairment: A double dissociation. Brain 114(Pt 5):2081-2094, 1991
21. Warrington EK, Shallice T: Category specific semantic impairments. Brain 107(Pt 3):829-854, 1984
22. Keller TA, Carpenter PA, Just MA: The neural bases of sentence comprehension: A fMRI examination of syntactic and lexical processing. Cereb Cortex 11(3):223-237, 2001
23. Caplan D, Alpert N, Waters G: Effects of syntactic structure and propositional number on patterns of regional cerebral blood flow. J Cogn Neurosci 10(4):541-552, 1998
24. Inui T, Otsu Y, Tanaka S, et al: A functional MRI analysis of comprehension processes of Japanese sentences. Neuroreport 9(14):3325-3328, 1998
25. Friederici AD, Ruschemeyer SA, Hahne A, et al: The role of left inferior frontal and superior temporal cortex in sentence comprehension: Localizing syntactic and semantic processes. Cereb Cortex 13(2):170-177, 2003
26. Humphries C, Love T, Swinney D, et al: Response of anterior temporal cortex to syntactic and prosodic manipulations during sentence processing. Hum Brain Mapp 26(2):128-138, 2005
27. Vandenberghe R, Nobre AC, Price CJ: The response of left temporal cortex to sentences. J Cogn Neurosci 14(4):550-560, 2002
28. Friederici AD, Meyer M, von Cramon DY: Auditory language comprehension: An event-related fMRI study on the processing of syntactic and lexical information. Brain Lang 75(3):289-300, 2000
29. Humphries C, Binder JR, Medler DA, et al: Syntactic and semantic modulation of neural activity during auditory sentence comprehension. J Cogn Neurosci 18(4):665-679, 2006

30. Schmahmann JD, Pandya DN: Fiber Pathways of the Brain. Oxford, England: Oxford University Press, 2006
31. Conturo TE, Lori NF, Cull TS, et al: Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci U S A 96:10422-10427, 1999
32. Basser PJ, Pajevic S, Pierpaoli C, et al: In vivo fiber tractography using DT-MRI Data. Magn Reson Med 44:625-632, 2000
33. Ciccarelli O, Toosy AT, Parker GJM, et al: Diffusion tractography based group mapping of major white-matter pathways in the human brain. Neuroimage 19:1545-1555, 2003
34. Mori S, Zhang J: Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 51:527-539, 2006
35. Mori S, Crain BJ, Chacko VP, et al: Three dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45:265-269, 1999
36. Klein AP: Diffusion tensor imaging atlas of the brain. In: Faro SH, Mohamed FB, Law M, Ulmer JL (eds): Functional Neuroradiology: Principles and Clinical Applications, (ed 1) New York, NY: Springer, 2011
37. Aralasmak A, Ulmer JL, Kocak M, et al: Association commissural, and projection pathways and their functional deficit reported in literature. J Comput Assist Tomogr 30(5):695-716, 2006
38. Maheshwari M, Klein AP, Ulmer JL: White matter: Functional anatomy of key tracts. In: Faro SH, Mohamed FB, Law M, Ulmer JL (eds): Functional Neuroradiology: Principles and Clinical Applications, (ed 1) New York, NY: Springer, 2011
39. Glasser MF, Rilling JK: DTI tractography of the human brain's language pathways. Cereb Cortex 18:2471-2482, 2008
40. Lazar M, Alexander AL: An error analysis of white matter tractography methods: Synthetic diffusion tensor field simulations. Neuroimage 20:1140-1153, 2003
41. Assaf Y, Pasternak O: Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. J Mol Neurosci 34:51-61, 2008
42. Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. N Engl J Med 2008(358):18-27, 2008
43. Berger M: Minimalism through intraoperative functional mapping. Clin Neurosurg 43:324-337, 1996
44. Duffau H, Capelle L, Sichez N, et al: Intraoperative mapping of the subcortical language pathways using direct stimulations: An anatomo-functional study. Brain 125:199-214, 2002
45. Duffau H, Gatignol P, Mandonnet E, et al: New insights into the anatomo-functional connectivity of the semantic system: A study using cortico-subcortical electrostimulations. Brain 128:797-810, 2005
46. Duffau H: The anatomo-functional connectivity of language revisited: New insights provided by electrostimulation and tractography. Neuropsychologia 46:927-934, 2008
47. Bello L, Gambini A, Castellano A, et al: Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. Neuroimage 39:369-382, 2008
48. Maldonado IL, Moritz-Gasser S, de Champfleur NM, et al: Surgery for gliomas involving the left inferior parietal lobule: New insights into the functional anatomy provided by stimulation mapping in awake patients. J Neurosurg 115:770-779, 2011
49. Maldonado IL, Moritz-Gasser S, Duffau H: Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study. Brain Struct Funct 216:263-274, 2011
50. Leclercq D, Duffau H, Delmaire C, et al: Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg 112:503-511, 2010
51. Dick AS, Tremblay P: Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. Brain 135(12): 3529-3550, 2012
52. Ungerleider LG, Haxby JV: 'What' and 'where' in the human brain. Curr Opin Neurobiol 4:157-165, 1994
53. Hickok G, Poeppel D: Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. Cognition 92:67-99, 2004
54. Hickok G, Poeppel D: The cortical organization of speech processing. Nat Rev Neurosci 8:393-402, 2007
55. Rauschecker JP, Tian B: Mechanisms and streams for processing of "what" and "where" in auditory cortex. Proc Natl Acad Sci U S A:11800, 2000
56. Rauschecker JP, Scott SK: Maps and streams in the auditory cortex: Nonhuman primates illuminate human speech processing. Nat Neurosci 12:718-724, 2009
57. Rauschecker JP: An expanded role for the dorsal auditory pathway in sensorimotor control and integration. Hear Res 271:16-25, 2011
58. Duffau H, Moritz-Gasser S, Mandonnet E: A re-examination of neural basis of language processing: Proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. Brain Lang 131:1-10, 2014
59. Duffau H, Herbet G, Moritz-Gasser S: Toward a pluri-component, multimodal, and dynamic organization of the ventral semantic stream in humans: Lessons from stimulation mapping in awake patients. Front Syst Neurosci 7:44, 2013
60. Catani M, Jones DK, ffytche DH: Perisylvian language networks of the human brain. Ann Neurol 57:8-16, 2005
61. Thiebaut de Schotten M, Ffytche DH, Bizzi A, et al: Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. Neuroimage 54:49-59, 2011
62. Makris N, Kennedy D, McInerney S, et al: Segmentation of subcomponents within the superior longitudinal fascicle in humans: A quantitative, in vivo, DT-MRI study. Cereb Cortex 15:854-869, 2005
63. Hua K, Oishi K, Zhang J, et al: Mapping of functional areas in the human cortex based on connectivity through association fibers. Cereb Cortex 19:1889, 2009
64. Tanabe H, Sawada T, Inoue N, et al: Conduction aphasia and arcuate fasciculus. Acta Neurol Scand 76:422-427, 1987
65. Yamada K, Nagakane Y, Mizuno T, et al: MR tractography depicting damage to the arcuate fasciculus in a patient with conduction aphasia. Neurology 68:789-790, 2007
66. Catani M, Piccirilli M, Cherubini A, et al: Axonal injury within language network in primary progressive aphasia. Ann Neurol 53:242-247, 2003
67. Breier JI, Hasan KM, Zhang W, et al: Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. Am J Neuroradiol 29:483-487, 2008
68. Davitian M, Ulmer JL, Mueller WM, et al: The superior longitudinal fasciculus and speech arrest. J Comput Assist Tomogr 32(3):410-414, 2008
69. Wakana S, Caprihan A, Panzenboeck MM, et al: Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage 36:630-644, 2007
70. Oishi K, Faria AV, Zijl PCM, et al: MRI Atlas of Human White Matter. New York: Academic Press, 2011
71. Catani M, Howard RJ, Pajevic S, et al: Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 17:77-94, 2002
72. Kier EL, Staib LH, Davis LM, et al: MR imaging of the temporal stem: Anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. Am J Neuroradiol 25:677-691, 2004
73. Martino J, Brogna C, Robles SG, et al: Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. Cortex 46(5):691-699, 2010
74. Dutton GN: Cognitive vision, its disorders and differential diagnosis in adults and children: knowing where and what things are. Eye 17:289-304, 2003
75. Ghika J, Ghika-Schmid F, Bogousslasvky J: Parietal motor syndrome: A clinical description in 32 patients in the acute phase of pure parietal strokes studied prospectively. Clin Neurol Neurosurg 100:271-282, 1998
76. Makris N, Meyer JW, Bates JF, et al: MRI-based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. Neuroimage 9:18-45, 1999
77. Tusa RJ, Ungerleider LG: The inferior longitudinal fasciculus: A reexamination in humans and monkeys. Ann Neurol 18:583-591, 1985
78. Habib M: Visual hypo-emotionality and prosopagnosia associated with right temporal lobe isolation. Neuropsychologia 24:577-582, 1986
79. Saur D, Kreher BW, Schnell S, et al: Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A 105:8035-8040, 2008

80. Wong FC, Chandrasekaran B, Garibaldi K, et al: White matter anisotropy in the ventral language pathway predicts sound-to-word learning success. J Neurosci 31:8780-8785, 2011
81. Rosenbaum RS, Winocur G, Moscovitch M: New views on old memories: Re-evaluating the role of the hippocampal complex. Behav Brain Res 127:183-197, 2001
82. Deweer B, Pillon B, Pochon JB, et al: Is the HM story on a "remote memory?" Some facts about hippocampus and memory in humans. Behav Brain Res 127:209-224, 2001
83. Saur D, Schelter B, Schnell S, et al: Combining functional and anatomical connectivity reveals brain networks for auditory language comprehension. Neuroimage 49:3187-3197, 2010
84. Yamada K: Diffusion tensor tractography should be used with caution. Proc Natl Acad Sci U S A 106:E14, 2009
85. Lopez-Barroso D, de Diego-Balaguer R, Cunillera T, et al: Language learning under working memory constraints correlates with microstructural differences in the ventral language pathway. Cereb Cortex 12:2742-2750, 2011
86. Menjot de Champfleur N, Lina Maldonado L, Moritz-Gasser S, et al: Middle longitudinal fasciculus delineation within language pathways: A diffusion tensor imaging study in human. Eur J Radiol 82:151-157, 2013
87. Cabeza R, Ciaramelli E, Olson IR, et al: The parietal cortex and episodic memory: An attentional account. Nat Rev Neurosci 9:613-625, 2008