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WHITE MATTER ARCHITECTURE OF THE LANGUAGE NETWORK

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Abstract

The relevance of anatomical connectivity for understanding of the neural basis of language was recognized in the 19th century, and yet this topic has only recently become the subject of wider research interest. In this paper, I review recent findings on white matter tracts implicated in language: the arcuate fasciculus, superior longitudinal fasciculus, extreme capsule, uncinate fasciculus, middle longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. The reviewed findings on these tracts were reported in studies that used a variety of methods, from post-mortem dissection and diffusion imaging to intraoperative electrostimulation with awake surgery patients. The emerging picture suggests that there is currently no consensus with regard to the exact number and identity of the tracts supporting language, their origins, trajectories, and terminations, as well as their functional interpretation.

Keywords

• White matter • Anatomical connectivity • Language • Dorsal stream • Ventral stream • Aphasia

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List of abbreviations

AF – arcuate fasciculus
BA – Brodmann area
DTI – diffusion tensor imaging
EC – external capsule
EmC – extreme capsule
IFG – inferior frontal gyrus
IFOF – inferior fronto-occipital fasciculus
ILF – inferior longitudinal fasciculus
MdLF – middle longitudinal fasciculus
MFG – middle frontal gyrus
MRI – magnetic resonance imaging
SFG – superior frontal gyrus
SLF – superior longitudinal fasciculus
STG – superior temporal gyrus
STS – superior temporal sulcus
UF – uncinate fasciculus
WM – white matter

1. Introduction

By connecting gray matter brain areas, white matter (WM) fiber tracts contribute to the formation of networks that afford emergence of cognitive processes. The left hemisphere temporo-perisylvian language network is one among several large-scale neurocognitive networks that have been identified so far in the human brain, along with the prefrontal executive function network, the fronto-parietal spatial network, the limbic/paralimbic network supporting explicit memory and motivation, the inferior temporal network supporting face and object recognition [1], and possibly the default mode network [2]. Large-scale networks consist of distant but interconnected local networks, which in turn are restricted to single cytoarchitectonic fields or adjacent areas [3].

Insufficient insight into the anatomical connectivity of the human brain, relative to more rapidly growing knowledge on brain's functional connectivity, has been repeatedly pointed out in literature as a major limitation in the current understanding of neurocognitive networks [4,5]. One reason for the still partial understanding of the brain's structural connectivity is the lack of powerful tools that would enable insights into the fine structure of WM. Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI) is a recently-developed imaging method that allows noninvasive *in vivo* studying of the brain's structural connectivity [6], complementing traditional research methods, such as post-mortem fiber dissection, histochemical tract-tracing, intraoperative electrostimulation, and conventional MRI [7]. Diffusion Tensor Imaging (DTI) provides an opportunity to study microstructural properties of WM by measuring the diffusion of water molecules within the tissue [8,9]. Typically studied DTI measures that are thought to indicate WM integrity are fractional anisotropy (FA) and mean diffusivity (MD). Changes in their values may indicate pathological processes; for instance, decreased FA and increased MD values are often found in the WM of Alzheimer's patients [10]. Other absolute diffusivities (radial and axial) as well as mode of anisotropy are less often reported in literature.

Unlike conventional T1-weighted MR images on which WM appears homogenous and does not allow differentiation among various WM structures, diffusion-based methods allow

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virtual *in vivo* dissection of WM, visualization of even smaller tracts [7,11], as well as estimates of the direction of axon fibers, which enables tractography [12]. This makes diffusion-based techniques an indispensable tool for studying the structural connectivity of the living brain [13]. Building on insights acquired by methods such as post-mortem blunt dissection and intraoperative electrostimulation, diffusion imaging techniques are currently demarcating new borders of knowledge on the complex architecture of WM, despite their often discussed limitations, such as spatial resolution, difficulty in interpreting orientation of mixing tracts within a voxel, and the risk of delineating structural connectivity maps that in actual fact may not correspond to anatomical connectivity [14-16].

The relevance of anatomical connectivity for understanding the neural basis of language was also recognized in the 19th century; for instance, to explain how brain damage caused speech disturbances in a 23-year old aphasic woman, Meynert [17] considered both affected grey matter areas and WM tracts. In the 1860s, Pierre Paul Broca established that injury in the inferior frontal gyrus (IFG) of the left cerebral hemisphere was associated with a profound speech loss [18]. Carl Wernicke found out that lesion in the left superior temporal gyrus (STG) was associated with impairment in speech comprehension [19]. In addition to distinguishing between two types of language disorders, presumably caused by lesions to these two respective brain areas — motor (or expressive) aphasia and sensory (or receptive) aphasia, Wernicke hypothesized that so-called conduction aphasia ("Leitungsaphasie") would result from injury to the WM fibers connecting the IFG and the STG. Namely, disruption of the anatomical connection between the IFG and STG, i.e. a fiber bundle known as the arcuate fasciculus (AF), would cause a disconnection between speech production and comprehension, which would lead to inability to repeat heard speech despite preserved comprehension and production. Conduction aphasia was subsequently confirmed clinically by Lichtheim, who further developed Wernicke's model [20]. Taken together, these developments shaped a model of the neural basis of language, according to which aphasia results not only from damage to the cortical grey matter areas supporting language function (IFG, STG), but also from a disruption of the connections between these areas (AF).

The Broca-Wernicke-Lichtheim's model had predominated over other language models for over a century. Its principles on the functional specialization of brain areas and importance of areas' connectivity for functionality represent the foundation of current models of the neural basis of language. Further development of the model was enabled among others by contributions such as Dejerine's work on anatomical connectivity towards the end of the 19th century and Geschwind's work, which in particular recognized the role of the inferior parietal region in language [21,22]. In recognition of Geschwind's contribution to the neuroanatomy of language, researchers working in this field sometimes refer to the inferior parietal region as "Geschwind's territory" [23].

With subsequent insights from studies involving brain-damaged patients and the advancement of neuroimaging, it has become clear that language is more distributed in the brain than previously thought [24-26]. Even Broca's historic patients Leborgne and Lelong, whose defining lesions were typically described as affecting the posterior third of the left IFG, have been discussed in light of new evidence obtained by CT and MR imaging of their brains that revealed more extended lesions [27,28]. In general, aphasia has turned out to be more complex than originally assumed. Returning to conduction aphasia for illustration, we find that lesions associated with this syndrome rarely affect only the AF [29], damage to the AF does not necessarily cause the syndrome [30], and that the syndrome may occur due to lesions in other brain areas, excluding the AF [21,31]. Furthermore, while successful speech repetition has been associated with intact left AF, this particular tract was found to be completely missing bilaterally in patient *S.*, who showed average sentence repetition ability and no conduction aphasia [32]. It appears that the anatomical and linguistic heterogeneity of conduction aphasia [33,34] cannot be explained by the classical language model. Regardless, the dorsal connection between Broca's and Wernicke's areas via the AF postulated in the early model has been incorporated in current models of the neural basis of language, although the classical view that a single WM tract connects anterior and posterior language areas had to be revised. Other WM tracts have been revealed to support various language functions, from naming and semantics to syntax, phonology, reading and writing.

2. The dual-stream model of language processing

Language is a higher cognitive function that brings together various processes, requiring executive resources and involvement of a range of brain areas. Language comprehension, for example, involves auditory/ visual word recognition, lexical and morphological processes, syntactic analysis or parsing, conceptual interpretation, referential processes, and so on [35]. The main processes involved in language production are conceptual processes, word selection and retrieval, sequencing at the sentence and word levels, articulation, and monitoring of speech output [25]. Being so complex, language is resource-demanding; for instance, a change in word order may require selective attention, whereas processes that heavily rely on temporary storage and manipulation of stored information, such as syntactic movement, may require additional working memory. Thus, researchers now focus on interactivity of anatomically distant brain areas that support various aspects of language functioning, rather than on functional specializations of isolated "language" areas [36].

Building on Wernicke's speech processing model, which involved two processing pathways stemming from the auditory system, on the one hand, and considering the dual-stream models of visual [37] and auditory processing [38], on the other, Hickok and Poeppel [39-41] have developed a dual-stream model for language (Fig. 1). According to their model, language processing begins with a spectrotemporal analysis supported by the auditory cortices in both hemispheres. Thus computed information moves to the phonological network in the middle to posterior portion of the cortex in and around the superior temporal sulcus (STS); information then moves via the dorsal stream, which is strongly left-lateralized and supports auditory-motor integration in speech processing, and the ventral stream, which is bilateral with a slight left hemisphere bias, and supports auditory comprehension. The dorsal stream in its posterior part involves a portion of the Sylvian fissure at the parietal-temporal boundary, supporting the auditory-motor interface; its anterior portion in the frontal lobe includes Broca's area and its surrounding, which, together with its more dorsal premotor component, supports processes relating sound to speech [40]. The ventral stream in its posterior portion (posterior middle and inferior portions of the temporal lobes) supports linking of phonological and semantic information (the lexical interface), while its more anterior areas support combinatorial semantic processes.

The dual-stream model does not consider the contribution of WM to language processing. It uses terms "stream" and "pathway" to refer broadly to information flow rather than as specific anatomical terms, which is common in functional neuroimaging studies [42]. In addition, recent fMRI findings on language comprehension and production indicate that an even more extended network of brain areas supports these functions [25,26]. With these details in mind, we turn to the specifics of WM tracts associated with the dorsal and ventral processing streams for language.

3. The dorsal stream: the superior longitudinal fasciculus fiber system

The major fiber tracts supporting the dorsal stream for language are the arcuate fasciculus (AF) and the superior longitudinal fasciculus (SLF). Although the term "arcuate fasciculus" is often used interchangeably with the term "superior longitudinal fasciculus" in older literature, the former term has become associated with the fibers originating from the temporal lobe, arching around the caudal part of the Sylvian fissure, and running to the frontal lobe, whereas the latter term has become associated with the fibers originating at the parietal lobe and coursing in the white matter above the Sylvian fissure to the frontal lobe [44]. In addition to evidence based on post-mortem dissection, the tracts have been identified using DTI tractography [45,46].

In terms of volume, the SLF is a major association fiber pathway in the human brain that interconnects frontal, temporal and parietal association areas. Due to its coursing through these regions, the SLF contributes to various associative and higher brain functions [47]. On the other hand, the AF is much smaller and appears to anatomically overlap only with a portion of the SLF. Research on the macaque monkey brain indicates that the WM bundle of fibers that originates in the superior temporal gyrus and its vicinity, arches around the caudal part of the Sylvian fissure and runs in the white matter above the Sylvian fissure to move dorsally, actually terminates in BA 8, which is not the predecessor of Broca's area [48]. Furthermore, a DTI study with 12 healthy human participants has shown that the rostral termination of the AF is in the precentral gyrus, not in Broca's area [49]. This evidence challenges the classical view, according to which the AF directly connects two core language areas, Wernicke's and Broca's, lending support to a model of language network in which the two core areas are interconnected over a "relay station", which is situated in the premotor or motor cortex [50]. In this view, the AF is more relevant to speech, as a motor function, than to language, as a cognitive function [49].

Anatomically, the SLF is considered a complex fiber system, consisting of three distinctive segments in the macaque monkey brain: SLF I, SLF II, and SLF III [44]. SLF I fibers originate from the medial and dorsal parietal lobe, run through the dorsal WM of the parietal and frontal lobe, and terminate in the supplementary motor area and dorsal BAs 6

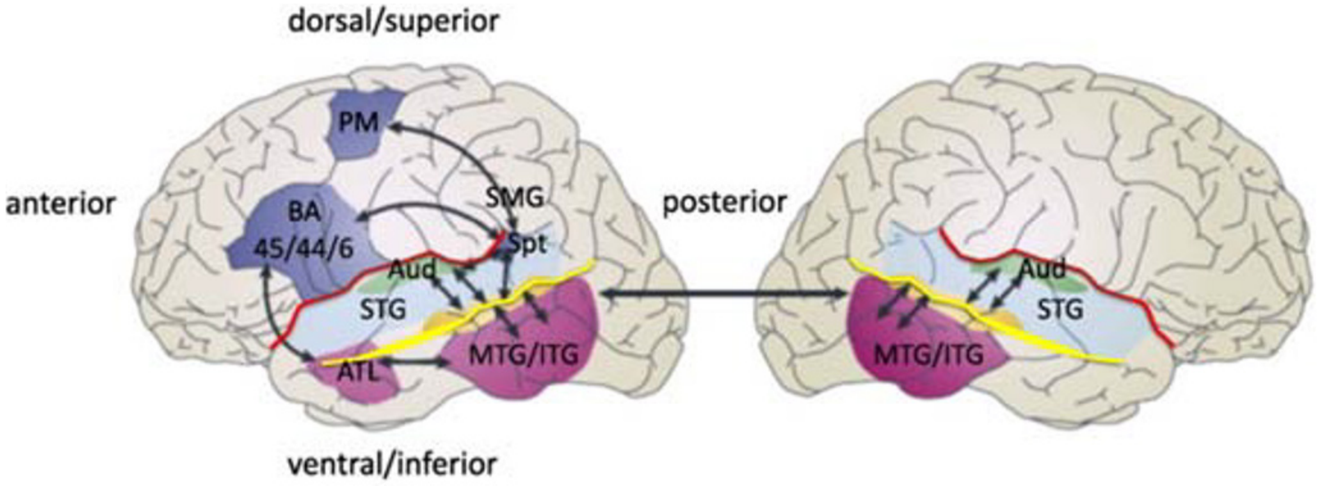


Figure 1.*Schematic of the functional anatomy of language processing Two broad processing streams are depicted, a ventral stream for speech comprehension that is largely bilaterally organized and which flows into the temporal lobe, and a dorsal stream for sensory-motor integration that is left dominant and which involves structures at the parietal-temporal junction and frontal lobe. ATL: anterior temporal lobe; Aud: auditory cortex (early processing stages); BA 45/44/6: Brodmann areas 45, 44, & 6; MTG/ITG: middle temporal gyrus, inferior temporal gyrus; PM, pre-motor, dorsal portion; SMG: supramarginal gyrus; Spt,Sylvian parietal temporal region (left only); STG: superior temporal gyrus; red line: Sylvian fissure; yellow line: superior temporal sulcus (STS). Adapted from (Hickok & Poeppel, 2007).*
Reprinted from Phys Life Rev. 6 (3), 2009, The functional neuroanatomy of language, Hickok, G., Fig. 1, [43], with kind permission from Elsevier.

and 8. SLF II fibers originate in the caudal part of the inferior parietal lobe, run in the WM above the Sylvian fissure and terminate in BAs 46, 9/46 and in the dorsal BAs 6 and 8. SLF III fibers originate from the rostral inferior parietal lobe, run through the rostral WM of the dorsal Sylvian operculum and terminate in ventral parts of BAs 6, 44, and 9/46 [51]. Since SLF III connects BA 44, which in the human brain represents the pars opercularis of the inferior frontal gyrus, and the rostral inferior parietal lobe, which in the human brain houses the supramarginal gyrus (BA 40), this tract in the human brain is predicted to have a role in language.

The tripartite model of SLF has been identified in the human brain using DTI. Since this technique does not always allow reliable determination of the fibers' origin and termination [52], they are extrapolated from research based on post-mortem dissection of the human brain or from findings on the non-human primate brain. Thus, the SLF connects the superior parietal lobe (SLF I), the angular gyrus (SLF II), and the supramarginal gyrus (SLF III) with frontal areas in the same hemisphere. In this model, the AF is considered a separate tract, which is within the SLF system labelled as SLF IV: it interconnects the superior temporal and middle temporal gyri with frontal areas [47]. Like in the non-human primate model, it is assumed that these pathways are bidirectional in humans.

In a comparative DTI study involving 10 live human subjects, three post-mortem chimpanzee brains and two post-mortem macaque brains, a strong connection via the AF connecting frontal cortex of the left hemisphere with the ipsilateral MTG and ITG was found in the human brain, but it was much weaker in chimpanzees and was not found in macaques [53]. Lack of projections of the AF fibers to the middle and inferior temporal gyri in monkeys was confirmed in another comparative anatomy study using spherical deconvolution tractography [46]. These findings have been interpreted to indicate changes in evolution of the connectional anatomy of the frontal lobes supporting higher cognition in humans, in particular language. Additional support for this view comes from the evidence on a strong leftward asymmetry of the AF in humans, which is consistent with left-hemisphere language lateralization typical for most right-handed people [23,54,55].

Another model of the dorsal structural connectivity for language focuses on the AF. It has been proposed that this set of fibers consists of two parallel pathways that connect frontal and temporal regions: a long direct pathway, which corresponds to the classical concept of AF connecting Broca's and Wernicke's areas, and an indirect pathway, which diverges into two segments [23]. The anterior indirect segment connects inferior parietal and inferior frontal areas, while the posterior indirect segment connects inferior parietal and posterior temporal areas. In this model, the direct segment is associated with automatic word repetition, whereas the indirect pathway is associated with auditory comprehension (the posterior segment) and vocalization of semantic content (the anterior segment) [23]. In other words, the long segment supports phonology-based language functions, whereas the indirect segment supports semantically-based language processes. Language disturbances such as acalculia and agraphia involve the anterior segment, whereas alexia implicates both anterior and posterior indirect segments. Furthermore, Wernicke's aphasia, nominal aphasia, and receptive aprosodia are associated with damage to the posterior and long segments, transcortical sensory aphasia with damage to the posterior segment, conduction aphasia with damage to the long segment, and Broca's aphasia with damage to the portion of the tract that runs underneath BAs 6, 44, 45 [56]. Damage to the anterior segment of the left AF has also been associated with non-fluent speech in aphasia [57].

Another DTI tractography-based two-segment model of the AF postulates that one segment of the tract terminates in the posterior STG, has a strong left hemisphere bias, and supports phonological processes, while the other segment terminates in the MTG, is also strongly left lateralized, and supports lexical-semantic processes [55]. Additionally, right hemisphere MTG terminations are associated with prosodic activations. Since DTI tractography provides information only on the anatomy of WM tracts, the proposed functions of the virtually *in vivo* dissected segments of the AF were extrapolated from functional neuroimaging studies of phonology, lexical-semantic processing, and prosody. The difference between Glasser and Rilling's [55] model and Catani *et al.*'s [23] model is that the latter assumes a larger area to be associated with semantic processing (BAs 39, 40 in addition to temporal areas), and that the STG and MTG pathways from the former model constitute in the latter model a single segment, which directly links to the frontal lobe and conveys phonology-related information. The model of Glasser and Rilling also suggests explanations of aspects of aphasia that elude the classical model [55].

The functional role of the arcuate has been controversial. Studies using different methodologies have confirmed that structural and functional integrity of the AF are critical for a range of language functions, not only speech repetition, as predicted by the classical arcuate model. For instance, intraoperative electrical stimulation of the AF during neurosurgical interventions in the awake patients showed that electrical stimulation of this tract generated anomia [58] and phonological paraphasias [59,60], whereas stimulation of WM corresponding to SLF III led to articulatory disturbances [60]. A study with 24 right-handed post-stroke aphasic patients showed that deterioration of the AF was associated with not only the patients' poor performance on phonological tasks, but also correlated well with their performance on tasks involving syntax and morphology [61]. Involvement of the dorsal language tracts in syntax was also suggested in a study with 27 patients with primary progressive aphasia (PPA), a degenerative disease that begins with language impairment, unlike Alzheimer's disease, where the earliest indicators of cognitive decline are memory disturbances. The study reported a significant association between the FA values in the SLF/AF and patients' deficits in comprehension and production of syntax; in contrast, the ventral tracts – the extreme capsule and the uncinate fasciculus (section 4) – were not significantly associated with the deficits [62]. However, this study does not distinguish between the SLF and the AF, reporting FA values that were quantified along the whole SLF system, which precludes inferences on which specific component(s) actually support(s) which aspect of syntax. Finally, the AF was shown to play a role in auditory verbal hallucinations in patients suffering from schizophrenia [63].

In the healthy brain, changes in microsctructure of the long segment of the AF, more specifically in radial diffusivity, have been associated with learning new words [64]. Learning to read, regardless of whether it took place in childhood or adulthood, has been associated with increased FA values in the posterior segment of the AF [65]. Another piece of evidence for this tract's role in reading comes from a study with a 15-year old female patient, *S.*, who had a missing AF in both hemispheres [32]. As a 5-year old child, this person underwent radiation therapy for a malignant brain tumor; radiation induced tissue necrosis, which affected cerebral white matter. At the time of testing, there were overall lower FA and higher MD values in the white matter throughout *S.*'s brain compared with the group of healthy control subjects. Crucially, while this person's oral language abilities were relatively spared, all aspects of her reading were affected, including reading of single words and non-words as well as text comprehension.

In summary, the notion of a single-tract dorsal connection between Broca's and Wernicke's areas that was represented by the AF in the classical language model has been challenged in light of evidence indicating more complex connectivity patterns. There is currently no consensus with regard to the exact anatomy and functionality of the dorsal WM tracts supporting language, but the AF and SLF III appear to support a wide range of language functions, from repetition, phonology, and syntax, to morphology, reading, articulation, and possibly others.

4. The ventral stream

Discrepancy of findings, which characterizes research on structural connectivity of the dorsal stream for language, also characterizes research on structural connectivity of the ventral stream. Debates involve issues ranging from those on which white matter tracts actually support the ventral stream, to issues on suggested tracts' origins, trajectories, and terminations, to their functional interpretability. Roughly, the ventral stream WM tracts interconnect the frontal brain areas with temporal and occipital areas implicated in language, including also the connectivity of the superior temporal and inferior parietal areas. Current literature suggests that the ventral stream for language may be supported by the extreme capsule (EmC), the uncinate fasciculus (UF), the middle longitudinal fasciculus (MdLF), the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF).

4.1 Extreme capsule

The EmC is a long association fiber pathway, which is comparable in size to SLF II. In the monkey brain, it interconnects the superior temporal sulcus, superior temporal gyrus, supratemoral plane and insula with BAs 45, 47, and dorsolateral prefrontal cortex [66]. It is located between the claustrum and the insula and separated by a thin layer of grey matter from the external capsule (EC), which is a strictly corticostriatal fiber tract located between the claustrum and putamen. DTI studies with humans report that the major portion of the EmC runs between the inferior frontal gyrus and the middle-posterior portion of the superior temporal gyrus, with some reports suggesting that it reaches into the inferior parietal lobe [67]. Given the role of these areas in language, it has been suggested that the EmC may represent a core language pathway [66-69].

However, the EmC is not always discernible from the external capsule when using DTI [70,71]. A recently published DTI atlas of human white matter, for instance, cannot discern the EmC from the EC and claustrum because of the scanning resolution used in data acquisition [7]. Nevertheless, Makris and Pandya [67] demonstrated that DTI allows this tract's fibers to be distinguished from the neighboring fiber bundles - the UF, the EC, the MdLF, the AF, the SLF II and III, and the ILF (Fig. 2).

Drawing on previous findings indicating that the mid portion of the STG is associated with language, while its posterior portion supports processing of sound location in space, as well as on the previous findings from their group [72] indicating that MdLF, rather than the posterior segment of the AF [23], connects the angular gyrus with the mid-portion of the STG, Makris and Pandya [67] argue that the EmC and MdLF (section 4.3) have a more prominent role in language than currently appreciated. For instance, they suggest that it is possible that the main dorsal connection between Broca's and Wernicke's areas is not the AF but actually the EmC. Note that, on this view, Wernicke's area is not situated in the posterior portion of the STG, as traditionally assumed, but rather in its mid portion. The model also relies on inferences from research on the monkey brain, suggesting that the connectivity between the areas in the monkey brain that are homologues to Broca's and Wernicke's areas is enabled by the EmC rather than the AF [66]. Evidence from studies by other research groups supports the view that the EmC is a critical ventral pathway that connects frontal (BA 45) and temporal (STG) language areas [69], and contributes to auditory comprehension [68]. In addition to supporting semantics, the EmC appears to also support syntactic comprehension - together with the AF, but it is not implicated in syntactic production, which is supported by the AF [61].

4.2 Uncinate fasciculus

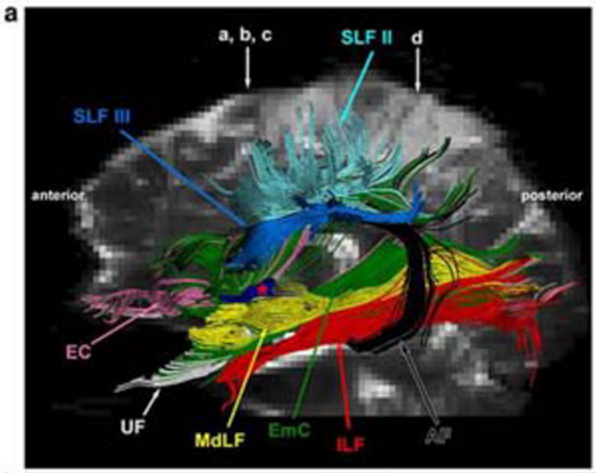
The uncinate fasciculus (UF) is a hook-shaped WM association tract that connects the anterior temporal lobe with the orbito-frontal cortex. In the monkey brain, it interconnects the most anterior part of the STG and the dorsal part of the temporal polar proisocortex with BAs 47/12, 13, the proisocortex of the orbital frontal cortex, and the medial prefrontal areas 25, 14, and 32 [48]. A DTI-based description of this tract in humans involves the frontal pole and orbital cortex as frontal lobe termination regions, and the temporal pole, uncus, hippocampal gyrus and amygdala as the temporal lobe termination regions [73].

The role of the UF in language is not clear. Due to strong connections of the orbito-frontal cortex and adjacent limbic areas with the amygdala – a key structure for regulation of affective responses – the UF may be implicated in the evaluation and regulation of responses to emotional auditory input [44,74].

Reduced FA values in this tract were found in patients with the semantic variant of primary progressive aphasia compared with healthy subjects [75]. Furthermore, reduced FA values and increased number of streamlines in this tract, which indicate the tract's deterioration, correlated with semantic deficits (single word comprehension and naming) in these patients. Evidence on a significant association between FA values in the UF of aphasic patients and their scores on tests of spoken word comprehension may also indicate this tract's role in semantic control, given that it connects areas that support cognitive control and areas supporting storage of word meanings [76].

Furthermore, the UF appears to be involved in proper name retrieval of famous people. An awake surgery study for the removal of a left hemisphere glioma (either frontal or temporal glioma) in 18 patients reported that, three months after the surgery, the patients with the UF resection were significantly impaired in naming famous faces and objects in comparison with patients without removal of the UF [77]. Patients with temporal glioma who underwent UF resection performed the worst, and patients with frontal glioma who underwent resection of the frontal portion of the UF performed worse than the patients with frontal glioma who did not undergo UF resection.

The UF may support other aspects of naming. An awake surgery study involving a patient with a tumor affecting the left insula, temporal stem and orbitofrontal cortex reported that intraoperative electrostimulation of the dominant UF during a picture naming task led to naming errors, verbal paraphasias (e.g., saying "fish" when naming a picture of a strawberry), and recurrent and continuous perseverations (unintentional repetition of the previous response instead of producing the target word) [78]. These errors suggest that the UF may support word production, retrieval of words from semantic memory, and inhibition of inappropriate words from short-term memory. Further evidence on the role of the UF in language semantics comes from a combined lesion-based and DTI study with 76 right-handed brain-damaged patients, which reports significant associations between FA values in



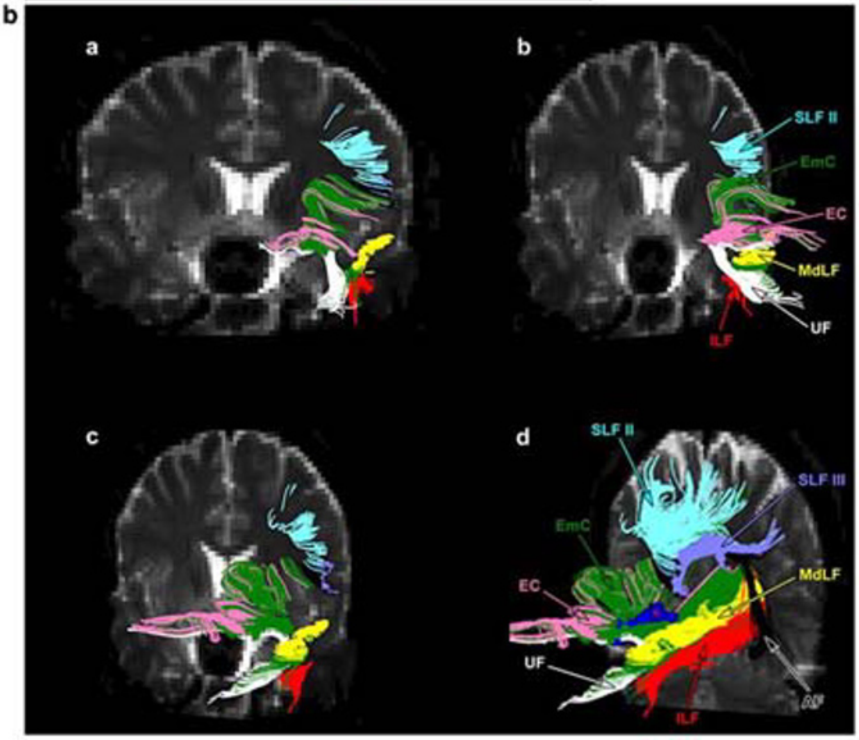


Figure 2a. *Composite topographic comparison of trajectories of EmC shown in green and a set of other fiber bundles on a T2-EPI left lateral profile using DT-MRI tractography. Using DT-MRI tractography, we [Makris & Pandya, 2009] were able to differentiate the EmC from other neighboring fiber pathways, i.e., the MdLF, EC, UF, AF, SLF II, SLF III, and the ILF. EmC (shown in green) is located laterally to EC (shown in pink). These two fiber pathways are separated by the claustrum, which is colored in dark blue and marked by a red asterisk. The claustrum was derived using the segmentation method (Filipek et al. 1994). The UF (shown in white) remains ventral to the EmC, whereas the AF (shown in black), SLF II (shown in turquoise) and SLF III (shown in blue) are located in a dorsal and lateral position with respect to the EmC. The ILF (shown in red) is situated in a ventral location in relation to the EmC.*

Figure 2b. *Four coronal sections (a–d) taken at two locations in the rostrocaudal dimension as indicated by arrows in a. The rostral arrow in a indicates the level of coronal sections a, b and c of* b*, whereas the caudal arrow in a indicates coronal d in b. The first three coronal sections, i.e., a, b and c, are the same coronal image shown at three different angles in order to visualize the different perspective of the individual fiber pathways. Abbreviations: AF arcuate fascicle; EC external capsule; EmC extreme capsule; ILF inferior longitudinal fascicle; SLF II and III superior longitudinal fascicles II and III; UF uncinate fascicle.*
Reprinted from Brain Struct Funct, 213, 2009, Makris, N. & Pandya, D.N., p. 348, The extreme capsule in humans and rethinking of the language circuitry, Fig. 5, [67], with kind permission from Springer Science and Business Media.

the left UF and patients' performance on three semantic tasks – oral picture naming, oral sound-based naming, and picture associative matching [79].

However, in an intraoperative electrostimulation study including 13 patients with gliomas affecting either the left anterior temporal lobe or the orbito-frontal area, subcortical stimulation of the UF did not lead to any language disturbances [59]. Furthermore, each patient had a portion of the UF removed and yet they all fully recovered language abilities after the surgery. Even though the scope of language testing in intraoperative stimulation is typically limited, and in this particular study it involved picture naming and counting (testing automatic speech production), the study findings indicate that the function of this tract in language may be compensated, which would mean that the UF does not represent a core language pathway [80,81].

4.3 Middle longitudinal fasciculus

The middle longitudinal fasciculus (MdLF) is a long association fiber tract that has been described in the human brain only recently [72,82], and its structure and function are already under debate. Originally described as a connection between the superior temporal and inferior parietal regions in monkey [83], this tract turned out to have similar, although more complex connectivity in the human brain [72]. A DTI study involving 39 healthy adults showed that, in addition to the STG and AG, this tract's connections include the temporal pole, superior parietal lobe, supramarginal gyrus, precuneus, and the occipital lobe [82]. Furthermore, the MdLF connections appear to be lateralized, with the left hemisphere MdLF connecting the temporal pole, STG, and AG, and the right hemisphere MdLF connecting the temporal pole, STG and superior parietal lobe. Based on these connectivity patterns of the MdLF, and considering the functional roles of the areas it interconnects, Makris *et al.* [82] proposed that this fiber tract supports language, auditory, visuo-spatial, and attention functions, with the left hemisphere MdLF supporting language-related and right hemisphere MdLF supporting attention-related functionality.

Results of another DTI study including six healthy subjects and using high-angular-resolution fiber tractography - a diffusion method more suitable for resolving fiber crossing than tensor-based models [15], indicate that MdLF mainly connects the STG with the superior parietal and occipitoparietal regions and only via minor and smaller connections with the AG [84]. Based on these findings, the authors argue that the MdLF tract may not be implicated in language per se, but instead it may function as a dorsal auditory pathway. Other tractography studies confirm that this tract connects the STG and the AG [85], and results from studies combining fMRI and DTI [68] as well as resting state-fMRI, DTI, and voxel-based lesion symptom mapping [86] indicate that the MdLF may be implicated in language comprehension.

The question whether MdLF is essential for language remains open. The methods used in the studies discussed above provide indirect evidence of this tract's structural connectivity. Direct evidence, obtained in intraoperative electrostimulation mapping in patients with glioma involving the left superior temporal gyrus suggests that MdLF - at least its anterior part - may not be essential for language [87]. Out of eight patients that underwent a surgery in which the anterior portion of this tract was removed, despite language disturbances observed immediately after the surgery in most cases, all but one patient recovered their preoperative language ability within three months after the surgery. While this finding indicates that the anterior part of the MdLF may not be critical for language, it leaves open the possibility that the posterior part of the tract may contribute to language. One must also keep in mind that the adult human brain retains the potential for plasticity and that the way in which the neural circuitry supporting language responds to glioma may reflect reorganization of the language network as a consequence of the brain's adaptation to illness. For instance, research on slow-growing lesions has shown that functional compensation following low-grade gliomas is considerably better than after acute lesions [88]. This leaves the possibility that the function of the MdLF may have been compensated in the patients with glioma involving the left STG who underwent resection of the anterior part of the MdLF [87], indicating that the MdLF may not belong to the core language tracts. Thus, the role of this tract in language remains unclear.

4.4 Inferior longitudinal fasciculus

The inferior longitudinal fasciculus (ILF) connects the occipital lobe with the temporal pole. It has been debated, however, whether this tract and the inferior fronto-occipital fasciculus (IFOF) (section 4.5) are two separate association fiber tracts or just one tract. Studies using different methods, such as cortex-sparing fiber dissection [89], DTI [86] and intraoperative electrostimulation [90] have demonstrated that these are two separate tracts. A way to anatomically disentangle the ILF from the IFOF was suggested as follows: the ILF runs "laterally and inferiorly to the lateral wall of the temporal horn. It is located just laterally and under the optic pathways, whereas the inferior occipitofrontal fasciculus [the IFOF] runs just medially and above the optic pathways. Thus, the roof of ventricle is a good anatomical landmark to distinguish between the ILF (below) and the inferior occipitofrontal fasciculus (above)" [91, p. 628].

Evidence for functional differentiation between the ILF from the IFOF comes from a study reporting a double dissociation on picture naming and reading. Picture naming requires object recognition before language semantic processing begins, while reading requires visual word recognition. An awake surgery study that combined preoperative DTI tractography and intraoperative cortico-subcortical electrostimulation mapping in three patients with lesions in the left basal posterior temporal areas reported that visual recognition and reading disturbances, but no disturbances in picture naming (i.e. semantic paraphasias), followed stimulation of the left ILF, whereas picture naming disturbances but no visual or reading disturbances followed stimulation of the left IFOF [90]. Thus, there is evidence indicating that the ILF and the IFOF are distinguishable both anatomically and functionally.

It has furthermore been debated whether the ILF forms a long association tract or an occipito-temporal projection system, i.e. a chain of U-shaped fibers connecting adjacent gyri and transmitting signals in a series of hierarchical steps, as argued for instance by Tusa and Ungerleider in the 1980s. The notion that there is no single direct tract running continuously from the occipital lobe to the temporal pole has recently been challenged by DTI and cortex-sparing fiber dissection findings that indicate the existence of both a direct ILF tract and an indirect, U-shaped bundle of short fibers connecting adjacent lateral occipitotemporal cortices [89,92].

The functional roles of the direct ILF and the occipito-temporal projection system in language are still not well understood. In general, impaired ILF has been associated with alexia, nominal aphasia, and reduced verbal fluency [56,93]. However, an intraoperative direct electrostimulation study of the ILF in 12 patients with a cerebral low-grade glioma in the left temporal lobe showed that neither direct stimulation nor resection of the left ILF, which is also called the "occipito-temporal fasciculus," affected these patients' naming ability [91]. In contrast, another awake surgery study reported that direct electrostimulation of this tract resulted in semantic paraphasias in 13 patients [59]. Thus, the ILF may represent an indirect ventral route for language, as signals may further be transmitted from the temporal pole via the UF to the orbito-frontal cortex, and also because it appears to allow compensation by the direct ventral route, i.e. IFOF [81,94].

4.5 Inferior fronto-occipital fasciculus

The inferior fronto-occipital fasciculus (IFOF) is a long association fiber tract that connects the occipital and frontal lobes, and which also contains fibers connecting the frontal lobe with the posterior parietal and temporal lobes [95]. However, the existence of an uninterrupted connection between the occipital and frontal lobes running through the inferior temporal lobe in the human brain has been questioned, as this tract has not been identified in the monkey brain [96]. Nevertheless, evidence from the human brain obtained using *in vivo* virtual [46,73,79,86,97] and post-mortem dissection [89,98,99] methods, as well as intraoperative electrostimulation with awake surgery patients [91] suggests the existence of the IFOF.

Using the Klingler fiber dissection technique, Martino *et al.* [98] dissected 14 postmortem human hemispheres and identified two components of the IFOF: a superficial and dorsal component, and a deep and ventral component. The former connects the frontal lobe areas with the superior parietal lobe and the posterior occipital lobe (superior and middle occipital gyri). The latter connects the frontal lobe with the posterior inferior occipital gyrus and posterior basal temporal areas. According to this study, the main posterior termination of the IFOF is the convexity surface of the posterior occipital lobe, but superior parietal lobe and temporo-basal areas were also identified. However, the study does not report the anterior tract's terminations, which were difficult to identify due to the intersection of this tract's fibers with the fibers within the lateral SLF and AF.

The two-layer anatomical model of the IFOF has been confirmed in other studies (e.g., in the cortex-sparing fiber dissection-DTI study by Martino *et al.* [89]) and further refined. For instance, based on results from a combined postmortem dissection (10 hemispheres) and DTI (one healthy participant) study, it has been suggested that the dorsal component of the IFOF terminates in the IFG, and that the deeper, ventral component of the IFOF consists of three subcomponents, all of which terminate in frontal/prefrontal areas [99]. The posterior subcomponent terminates in the middle frontal gyrus and dorso-lateral prefrontal cortex, the middle subcomponent terminates in the MFG and orbito-frontal cortex, and the anterior subcomponent terminates in the orbito-frontal cortex and frontal pole. A study using a q-ball residual bootstrap reconstruction of High-Angular Resolution Diffusion Imaging (HARDI) involving 20 healthy subjects also suggests diffuse IFOF projections in the frontal lobe: orbito-frontal region, inferior frontal (BAs 47, 45), rostral portion of the middle frontal (BAs 10, 46) and superior frontal gyrus (BAs 8, 9) [100].

The IFOF connectivity involves, among others, the regions of the brain that are highly implicated in language, such as the left inferior frontal areas, temporo-parietal, and the ventral occipitotemporal region; thus, it is reasonable to postulate that this tract plays a role in language. More specifically, the IFOF has been suggested to support semantics, reading and writing. Evidence from awake surgery studies involving patients with cerebral gliomas in the dominant hemisphere and using intraoperative subcortical electrostimulation reveals that this tract is implicated in semantic processing [91,101]. A DTI study with 76 brain-damaged patients showed significant associations between the patients' performance on semantic tasks (oral picture naming, oral sound-based naming, and picture associative matching) and FA values in the IFOF [79]. Based on the findings from this study, it has been suggested that the surface layer of the IFOF may support bridging of the semantic memory with the verbal system, and that the deep layer of the IFOF may be critical for object semantic processing.

Other possible contributions of the IFOF to language pertain to reading and writing [102]. A DTI study with patient *S.*, who missed the AF bilaterally, reported that the IFOF was intact in this patient [32]. Her reading deficit clearly could not have been compensated for via an alternative, ventral reading route (supported by the IFOF). Namely, in skilled readers, two reading routes complement each other - the phonological (or grapheme-phoneme conversion) route and the orthographic (or reading by direct word access) route. Similarly, a recent DTI study that investigated the WM connectivity of the reading network in 20 adults with dyslexia reported no significant differences in FA values in the IFOF in this group compared with the control group (significant group differences were reported for the orthographic processing, i.e., at the behavioral level) [97]. In contrast, significant group differences were found in FA values in the direct segment of the AF, which supports the dorsal reading route. However, despite the lack of structural abnormalities in the WM microstructure of the IFOF in the group with dyslexia, as indexed by FA values, significant correlations were found between the orthographic processing and FA values in the left IFOF in this group. Thus, these results provide some evidence for relatedness of the ventral reading route and the IFOF.

Further evidence on the IFOF's contribution to reading comes from an intraoperative stimulation study combined with post-surgical DTI. This case study involved a Japanese patient who underwent awake surgery for resection of a left inferior parietal lobe glioma [103]. Intraoperative direct subcortical stimulation revealed the patient's poor performance on a picture naming task (resulting in semantic paraphasias), oral reading task involving Kanji, i.e. ideograms, representing whole words, and Kana, i.e., phonograms, representing sounds (resulting in alexia), and a writing task involving Kanji (resulting in agraphia). The patient did not have difficulties with speech repetition. Subsequent reconstruction of WM tracts at the site of tumor resection indicated the involvement of the dorsal IFOF in reading and writing. Considering the model in which the phonological reading route is supported by the AF and the lexical route by the IFOF, one would expect the reading deficit associated with the IFOF not to involve Kana or that a deficit in reading Kana (phonological route) would be associated with damage to the AF, instead of the IFOF. However, that was not the case, despite the anatomical proximity of the AF to the surgical cavity.

Taken together, this evidence suggests involvement of the left IFOF in language processes. The tract, however, remains controversial. Some researchers argue that the existence of the IFOF in the human brain may represent an anatomical precondition for the development of higher cognitive functions in humans [104]. Others believe that the IFOF and the EmC may represent the same tract, suggesting that choosing to speak of the IFOF instead of the EmC may be more suitable when discussing the language network and its functionality [81,105].

4.6 Summary of the ventral stream

Several WM tracts have been described as supporting the ventral processing stream for language: the EmC, UF, MdLF, ILF, and the IFOF. The ventral tracts appear to support a range of language functions, such as naming and semantics, syntax, reading, and writing. Clearly, more research is needed to reveal the full range of language-related functions that these tracts may support. Furthermore, there is currently no agreement on which of these tracts is critical for language. One prominent model postulates a direct and an indirect ventral pathway for language, represented by the IFOF and the ILF respectively [80,81]. The model considers the EmC and the IFOF as "conceptually same," dispensing with the EmC. The indirect pathway, the ILF, relies on the UF for supporting continuation of signal transmission from the temporal pole to frontal areas. The model assumes a degree of subcortical plasticity within the network, as the function of the indirect pathway may be compensated by the IFOF in case of damage. Finally, the MdLF is not considered critical for language in this model.

5. Conclusion

Connectivity patterns in the brain contain important information on the functioning of intact and damaged brains [21]. Connectivity patterns associated with language have become an object of growing interest in a wider research community due to recent methodological advancements involving DTI and fMRI methods. New developments have enabled a considerable departure from the classical language model, which posits that Broca's area (BA 44, 45), Wernicke's area (posterior BA 22), and the AF represent the main components of the language network. More recent evidence indicates that language computations are much more distributed in the brain, with additional grey matter areas and additional WM tracts contributing to language function. The currently dominant view is that "there are no 'centers' dedicated to comprehension, articulation, or grammar but a distributed network in which nodal foci of relative specialization work in concert" [3]. On this view, a way to address brain connectivity patterns is by determining the properties of hubs, ancillary nodes, and their connections within a network [106-109].

It appears that, along with growing knowledge on the functional anatomy of language, understanding of the structural anatomy of language is also growing. However, findings on WM tracts implicated in language are often discordant and there is currently no consensus with regard to the exact number and identity of WM tracts subserving language, their names, their origins, trajectories, and terminations, or their functional interpretation. Moreover, a coherent framework for studying the neural basis of language that would systematically incorporate the contribution of WM to the language system is still missing [110]. In addition to the dorsal and ventral pathways for language, research on language WM has also recognized a visual language stream, a striatal-control stream and a motor stream [80,81,111]. Future efforts to expand knowledge on the language connectome need to include further investigation of these pathways.

For instance, several studies reported new frontal lobe WM tracts connecting to Broca's area, indicating their possible role in speech production. Since the eponym Broca's area has been used in an inconsistent way, indicating most of the time BAs 44 and 45, but sometimes only BA 44, or some combination of areas 44, 45, 46, 47 and 6 [112], it is important to provide clear anatomical definitions when using the terms Broca's area and Wernicke's area [113], in particular when attempting to infer the functional contribution of WM tracts terminating in such areas. Assuming that Broca's area comprises BAs 44 (pars opercularis), 45 (pars triangularis), and 47 (pars orbitalis), a recent DTI study involving 12 healthy subjects defined two new tracts interconnecting these areas [114]. One is the operculo-premotor fasciculus, which is a bundle of U-shaped fibers that connects BA 44 with the premotor region. The other is the triangulo-orbitalis system, which contains U-shaped fibers connecting BA 45 and BA 47. Given the areas they connect, on the one hand, and the fact that these tracts have not been observed in the non-human brain on the other, their involvement in language seems plausible. Another study that combined fiber dissection and DTI tractography [115] also discerned frontal intralobar tracts with a possible role in language. More specifically, it identified an association fiber tract connecting BAs 44 and 45 with the lateral SFG, which was named Broca-lateral SFG tract. Finally, it has been proposed that the frontal aslant tract (FAT) also contributes to language. This tract connects BAs 6 and 44 in the inferior frontal gyrus with BAs 8 and 6 in the SFG [46]. However, anatomical descriptions of this tract's origin report different areas [111]. Using post-mortem blunt dissection and diffusion tractography based on spherical deconvolution, Catani *et al.* [116] determined that the FAT connects BA 44 and the anterior supplementary and pre-supplementary motor area of the SFG, and that some fibers reached BA 45 and the inferior part of the precentral gyrus (Fig. 3).

Possible functional roles of the FAT in language include motor planning, vocalization, and speech [46]. For instance, this tract was compromised in patients with PPA, as indicated by changes in FA and number of streamlines. Furthermore, these changes correlated with a verbal fluency decline in the patient group [75]. Crucially, verbal fluency was assessed in this study on the basis of collected speech samples, and not on letter- or category-cued fluency test. Thus, in addition to the dorsal and ventral language tracts, intralobar interconnectivity of frontal areas, i.e. the anterior system stemming from Broca's area, is emerging as also relevant for language (speech production).

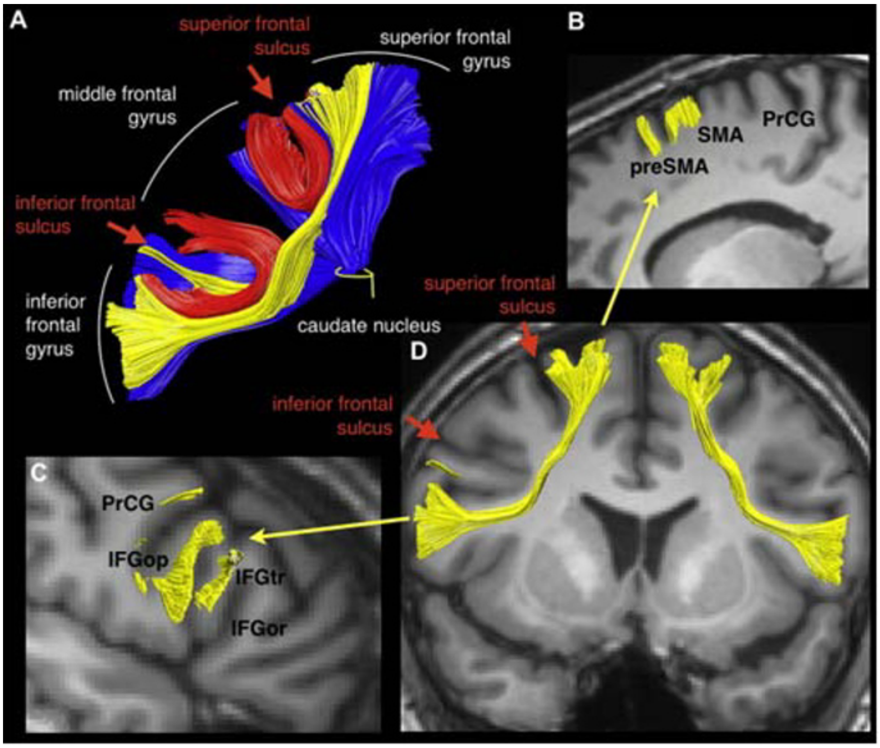


Figure 3. *A) Connections of the premotor regions of the frontal lobe. The frontal aslant tract (FAT) (yellow) connects the B) dorsal and medial (supplementary and pre-supplementary motor area, SMA and pre-SMA) cortex of the SFG with the C) posterior region of IFG. Red U-shaped tracts connect the superior and middle frontal gyri and the inferior and middle frontal gyri. Blue projection fibres connect the cortical premotor regions with the head of the caudate nucleus. D) The frontal aslant is a bilateral tract (for the lateralization analysis see Fig. 9). Reprinted from Cortex, 48, 2012, p. 280, Short frontal lobe connections of the human brain, Catani, M., Dell'Acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., Valabregue, R. & Thiebaut de Schotten, M., Fig. 5, [116], with kind permission from Elsevier.*

Throughout this review, strengths and limitations of the methods used in the reported studies were also briefly discussed. For instance, DTI represents a major methodological improvement in studying the brain, because it allows noninvasive *in vivo* dissection of WM structures. The fact is, however, that this method cannot reliably define origins and terminations of WM tracts, requiring therefore validation by complementary methods. Moreover, it may lead to generation of false results, indicating the existence of nonexistent tracts and not recognizing existing tracts. False negatives are in particular problematic in tractography for surgical targeting [117]. Intraoperative stimulation with awake surgery patients has excellent potential to contribute to better understanding of WM connectivity for language. However, for obvious reasons it allows only a very short time for intraoperative testing, during which a limited number of tests of language functionality are used. Typically used tests are picture naming and counting, although repetition, reading and writing have also been tested in some studies. These tests cannot assess the full scope of possible language impairment. In addition, intraoperative testing during awake surgery is normally performed with patients undergoing a tumor resection, which raises the possibility that language functionality may be affected by the brain's adapting to illness. Finally, intraoperative brain mapping is restricted to a surgical area, which precludes testing of the whole network [90]. Thus, to provide a better insight into anatomical connectivity of language, future research needs to rely more on using combined anatomical (DTI *in vivo* and post-mortem dissection) and functional (intraoperative subcortical stimulation) methods.

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