Clinical value of mapping the language network with MR diffusion tractography

Alberto Bizzi, M.D.
Neuroradiology Unit
Istituto Clinico Humanitas IRCCS
Milan, Italy

The aim of surgery in Neurooncology is to achieve maximal tumor cytoreduction while avoiding postoperative neurological deficits. In order to achieve this goal it is mandatory not only to preserve eloquent cortex but also to safeguard indispensable white matter pathways. Intraoperative direct subcortical ESM is the method of choice to map functional boundaries of the resection cavity and it has significantly improved the survival rate of patients undergoing resection of low-grade gliomas(1).

Diffusion MR tractography has recently emerged as a valuable clinical tool for presurgical planning(2-4) and intraoperative imaging-guided navigation in the operating room(5). Diffusion MR tractography has the potential to provide unique information about connectional anatomy and pathology-induced changes. This information has not been available before and it can be acquired with clinical 1.5 and 3 tesla MR units. Despite several challenges and limitations inherent to current diffusion imaging methods(6), the information provided by tractography is good enough to be used in the clinic. Currently tractography is a user-dependent method. The challenges, limitations and pitfalls(7) must be understood carefully before interpreting the results of tractography for presurgical planning. Useful imperfect and user-dependent tests are used in the clinic everyday all the time.

The language network

Modern theories about brain functional organization suggest that high cognitive systems are organized in widespread, segregated and overlapping networks(8), rather than single cortical areas. Thus, it is important to understand how brain regions are linked within large-scale networks and to map lesions onto connecting white matter tracts. A synopsis of classical neurological syndromes associated with frontal, parietal, occipital, temporal and limbic lesions has been provided to facilitate this network approach(9).

Recently Hickok & Poeppel have proposed a model of the language network with two broad processing streams connecting an anterior language center located in the inferior frontal opercular region (Broca area) with a posterior center in the posterior temporal (Wernicke area) and inferior parietal regions(10, 11). According to

this dual system model a stream running dorsally to the sylvian fissure via the *arcuate fasciculus* (AF) is involved in mapping sound onto articulatory-based representation whereas a stream coursing ventrally in the temporal lobe, temporal stem and orbital part of the frontal lobe is involved in mapping sound onto meaning. According to this model language emerges through the interaction of multiple neocortical nodes in the frontal operculum, posterior third of the temporal lobe and inferior parietal lobule of the dominant hemisphere.

A dual stream system has also important implications for understanding the adaptive processes involved during development of a slow growing focal brain lesion such as a low-grade glioma. A parallel processing system with dorsal and ventral pathways offers many options for compensatory and adaptive (plasticity) mechanisms after acute or subacute lesions. This model should help to better understand the complexity of aphasic syndromes and mechanisms of recovery from aphasia(12).

Several important issues remain to be addressed: the anatomic course and cortical projections of the two pathways, the function of each tract, its importance, essentiality (i.e. eloquence) and vulnerability in reference to the functionality of the network.

Mapping connections in the language network

Four main techniques are currently available to map the tracts of this dual system: axonal label tracing methods in monkeys, ex-vivo postmortem dissections, in-vivo MR tractography with diffusion tensor imaging (DTI) and intraoperative direct subcortical ESM in humans. Despite current limitations of each technique, the concordance between the three methods used in humans is good.

The dorsal pathway

In humans the AF and the superior longitudinal fasciculus (SLF) have long been considered synonymous and the names have been used interchangeably. Recent DTI MR tractography studies have contributed to this confusion in terminology. In the monkey the SLF comprises three segments (SLF I, II and III) connecting the parietal-occipital lobes with the prefrontal areas. In humans the AF visualized with deterministic DTI MR tractography connects the posterior superior and middle temporal gyri with the neocortex in the anterior (pars opercularis, BA44) and posterior (ventral precentral gyrus, BA6) banks of the ventral precentral sulcus. According to deterministic DTI MR tractography results the AF does not project into the pars triangularis (BA45) and orbitalis (BA47) of the inferior frontal gyrus (IFG)(13). If more advanced diffusion imaging methods are used (i.e. spherical

deconvolution or Q-ball) few streamlines may project into pars triangularis and orbitalis, however these results have not been validated yet.

DTI MR tractography studies are showing that the anatomy of the perisylvian dorsal pathway is more complex than previously thought. Catani et al.(14) virtually dissected three segments of the AF using two-ROIs seeding with a deterministic approach: a direct pathway connecting "Broca territory" with "Wernicke territory" (long and medial segment) and an indirect pathway subdivided in two segments: an anterior segment connecting the premotor cortex (ventral and dorsal BA6) with the inferior parietal lobule; and a posterior segment connecting the inferior parietal lobule with the posterior temporal region (MTG/STS). Post-mortem dissection in human have confirmed the existence of the three segments of the AF(15).

The ventral pathway

Determination of the tracts involved in the ventral pathway is still a matter of debate(12, 16, 17). Some authors have suggested that the inferior frontal occipital fasciculus (IFOF), uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) are components of the ventral pathways, whereas other investigators have suggested that bundles coursing along the extreme capsule (EmC) between the insular cortex and the claustrum are critical(18). It is important to remark that the temporal stem may be the critical segment of the ventral pathway connecting the temporal with the frontal lobe(19). The UF, IFOF and EmC cross the temporal stem, a narrow structure coursing immediately above the middle cerebral artery(20). A complete surgical resection of the temporal stem in the dominant hemisphere would disconnect the temporal and frontal lobe language networks.

A brief description of the tracts of the ventral pathway virtually dissectable with DTI MR tractography has been provided with a 3D atlas(21, 22).

The *IFOF* is an associative bundle with long and short fibers that connects the ventral part of the occipital lobe with the medial part of the temporal lobe and the orbitofrontal cortex. In the temporal stem the IFOF runs dorsally and medial to the uncinatus. Along his course the IFOF runs parallel and medially to the ILF(23). Its functions may be related to reading, attention and visual processing.

The *UF* is an associative bundle connecting the anterior temporal lobe with the medial and lateral orbitofrontal cortex(23). It was described by Dejerine(24). In the temporal pole the UF is lateral to the amygdala and hippocampus, then curves upward, passing behind and above the trunk of the middle cerebral artery into the temporal stem. From there, it continues into the posterior orbital gyrus. It is considered to belong to the limbic system but its functions are still poorly understood. Recently it has been shown that surgical resection of the UF (either in its

frontal or temporal part) has long-lasting consequences for famous face naming(25). The authors have suggested that it is part of a circuitry involved in the retrieval of word form for proper names.

The *ILF* is an associative bundle with long and short fibers connecting the occipital and temporal lobes. The long fibers connect the amygdala and hippocampus to the visual areas(23). The ILF is involved in face recognition, visual perception, reading, visual memory and other functions related to language.

In the monkey the *EmC* connects superior and middle temporal gyri and rostral part of the insula with the pars triangularis (BA45) and pars orbitalis (BA47)(26). This fronto-temporal connection may relay in the insula and claustrum. A role of the rostral part of the insula in motor planning of speech has been demonstrated in stroke patients with articulatory planning deficits and left precentral insular gyrus infarct(27).

Although language lateralization has been well established, its anatomical basis is not fully understood. In particular, the role of the UF, IFOF and ILF in maintaining the integrity and functionality of the language network has been elusive. Intraoperative direct cortical and subcortical ESM data seem to support the hypothesis that the IFOF in the dominant hemisphere is likely implicated in language specialization(28, 29). Interestingly, in another intraoperative study subcortical ESM of the left ILF never elicited any language disturbances(30). In addition, all patients recovered following a transient postoperative language deficit, despite the resection of at least one part of the ILF. This study seems to suggest that the ILF may not indispensable for language. On the contrary, evidence for a role of the ILF in object naming was provided by the single case of a patient with glioma infiltration of the left temporal lobe and IFOF disruption prior to tumor invasion(31).

Challenges of MR tractography for brain surgery

Diffusion MR imaging provides unique insights into both macrostructure and microstructure. Water molecules move preferentially along the bundle of parallel axon and diffusion imaging reveals the dominant orientation of these bundles. In the proximity of a tumor, white matter bundles can be displaced, infiltrated, diluted by vasogenic edema, or destroyed(32). Diffusion anisotropy is typically reduced in areas of tumor infiltration and/or vasogenic edema. Preliminary validation studies of DTI MR tractography with intraoperative ESM have shown that false negative results may be found in the proximity of infiltrating low-grade glioma(33-35).

It is important to remark that tractograms are virtual estimation (streamlines) of the orientation of white matter bundles. The estimate depends on the microstructural properties of the tissue. The degree of uncertainty of the estimate is

reduced in anatomical and pathological conditions: in voxels with more than one bundle (such as in the deep fronto-parieto-temporal white matter at the crossroad between the corticospinal tract, corpus callosum and SLF) and in voxels with increased free water content secondary to tumor infiltration or edema leading to apparent reduced anisotropy. The former type of challenge can be overcome with advanced diffusion methods such as high angular resolution diffusion imaging (HARDI)(36) and constrained spherical deconvolution (cSD)(37) which have the ability to extract multiple orientations of fibers in voxels containing more than one bundle. The latter type of challenge can be overcome with advanced imaging methods able to separating diffusion properties of the bundles from surrounding free water. Implementation of new advance methods such as Noddi(38), CHARMED(39), AxCaliber(40) and ActiveX(41) should offer a new class of microstructural tissue parameters, such as mean axonal diameter, that may give a more specific estimation of regional changes than measures derived from DTI. In the future implementation of the new methods in the clinics may have the potential to generate more reproducible, less user-defined tract reconstruction in patients with glioma.

Clinical value of MR tractography

Several important issues are the focus of current basic and clinical research: function, importance, vulnerability and indispensability of each pathway in reference to network functionality. Gliomas infiltrating the perisylvian region on the dominant hemisphere offer a unique opportunity to identify gray and white matter structures that are essential for speech production. In a study on 19 right-handed patients it was shown that gliomas growing in the ventrolateral aspect of the left frontal lobe may cause mild to moderate speech deficits. Gliomas growing in the left VPCG were much more likely to cause speech deficits than gliomas infiltrating the IFG, including Broca area. MR DTI tractography was valuable to demonstrate that lesion extension to the AF was a requisite for the appearance of aphasia in brain tumor patients(42). Patients with glioma infiltrating either the IFG or the VPCG without involvement of the AF-direct segment did not show conduction aphasia (Figs. 3-5).

A prominent role for the insula in speech production has been suggested by an MRI study in 25 stroke patients with a deficit in motor planning of articulatory movements(27). All patients with the deficit had lesions that included a discrete region of the dominant precentral gyrus of the insula, but not all had a lesion in pars opercularis. This area was completely spared in other 19 stroke patients without these articulation deficit. fMRI studies have confirmed the important role of the

insula for motor planning of speech. However, patients with diffuse LGG infiltrating the insula, the temporal stem and the anterior temporal region have normal scores on language tests despite large tumor size (Bizzi A, personal communication).

Integration of Diffusion MR tractography in the operating room

Three dimensional objects of preoperative virtually dissected tracts can be reliably integrated into a standard neuronavigation system, allowing for intraoperative visualization and localization of the main tracts(43). MR tractography may show the relationship of the mass to the virtually dissected AF, IFOF and CST. Virtual dissection of main tracts may help to evaluate whether the mass has interrupted, infiltrated or displaced the tract of interest. Low grade gliomas tend to infiltrate tracts, while high grade gliomas usually displace or interrump them. Display of MR tractograms on the neuronavigational device in the operating room is valuable when the neurosurgeon is evaluating the distance of a specific tract from the surgical cavity and he uses subcortical ESM to test its functional relevance(33).

In conclusion, fMRI and DTI provide unique information that has been changing presurgical evaluation of patients with brain gliomas, and in particular when the mass is located nearby eloquent areas. Virtual dissection of the major white matter tracts should be used only as a road map for presurgical planning and as guidance for intraoperative subcortical ESM.

Clinical studies with MR diffusion tractography are showing that lesion extension to the white matter pathways (i.e. AF and IFOF) connecting frontal to parietal and temporal speech regions is an important mechanism for the appearance of aphasia.

More advanced diffusion imaging methods such as Noddi and Spherical Deconvolution are being implemented to meet the challenges of presurgical planning in patients with a brain tumor.

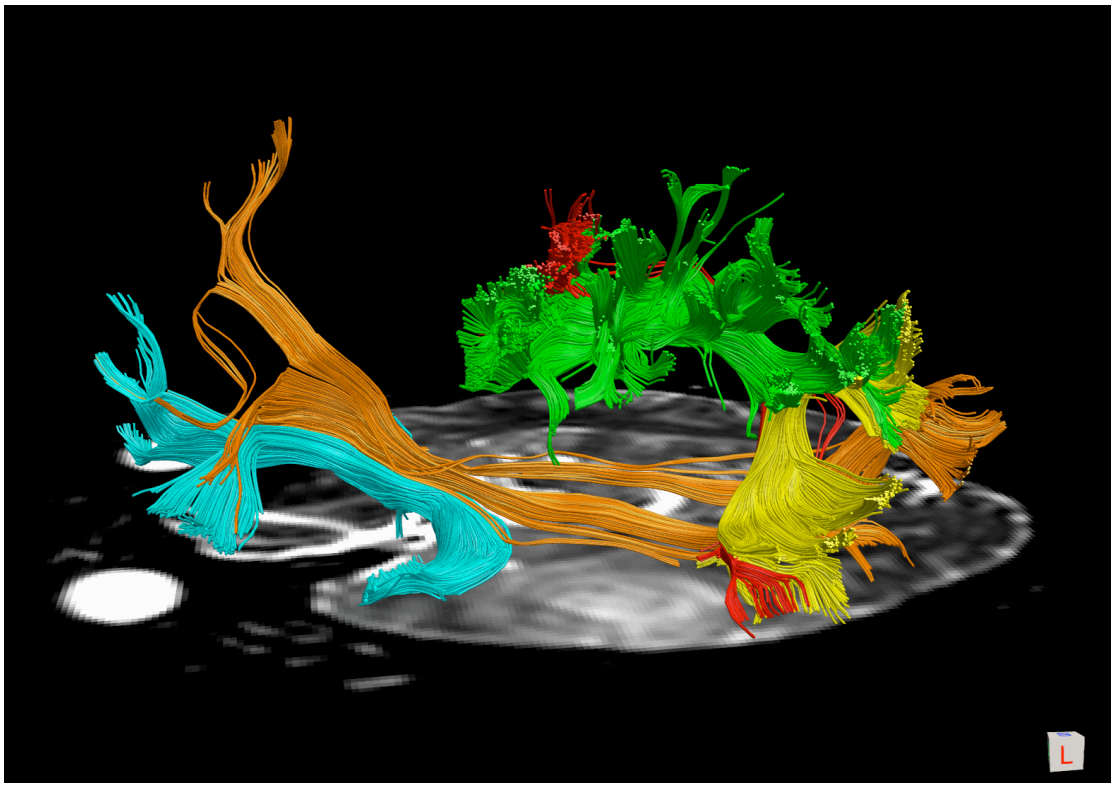

Figure 1 – Virtual dissection with deterministic DTI MR tractography of the dorsal (AF) and ventral (IFOF and UF) language pathways in a patient with anaplastic oligoastrocytoma infiltrating the inferior part of the left temporal lobe. The tumor had infiltrated the ILF. The patient had no preoperative and postoperative language deficits on the Aphasie Aachen Test. The relation of the tumor with the three segments of the AF (direct in red, anterior in green, posterior in yellow), the IFOF (in orange) and UF (in cian) are illustrated. Note that the UF and the IFOF tracts course respectively along the anterior and medial boundary of the tumor; the AF is only mildly displaced dorsally by the mass effect.

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