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fMRI and Tractography for Clinical Applications

Andreas J. Bartsch, MD
Department of Neuroradiology, University of Heidelberg & FMRIB Centre, University of Oxford

I. Introduction

This talk and the accompanying syllabus contribution provide a brief overview of the clinical application of fMRI and diffusion tractography. Attendees will get an impression how clinical fMRI and tractography have fared over the past decade, what their limitations are and what needs to be done to substantiate their specific merits in the future. For this purpose, I will only focus on those applications that have been translated into medical practice and already exert an impact on actual clinical decision-making for individual patients. As yet, such applications of fMRI and diffusion tractography are exclusively examinations dedicated to the presurgical assessment, planning and intra-operative neuronavigation. Their goal is *i)* to preserve relevant cortical areas and fibre pathways from surgical damage upon resection of brain tumors, other intra-axial CNS lesions and epileptogenic foci or *ii)* to confirm residual stimulability of the auditory system and integrity of its afferent pathways prior to cochlear or auditory brainstem / midbrain implantation.

II. Specific Clinical Applications and Associated Methodological Issues

Mapping and tracking prior to resective surgery constitute the mainstay and most frequent incentive for clinical fMRI and tractography applications. In this context, fMRI and tractography promise to localize functionally relevant cortical areas and fibre tracts. Given that fMRI and diffusion-weighted imaging (DWI) measure only epiphenomena of neural activity and axonal integrity, both methods are susceptible to false-negative (FN) results. FNs are generally what the clinician most worries about because what the neurosurgeon wants to infer from fMRI and / or diffusion tractography is information on how to access brain tumors, other intra-axial CNS lesions or nonlesional epileptogenic foci, if these can be safely re- (or trans-)sected in total or just to a partial degree and what deficits must be expected as a result of the procedure. Unfortunately, the blood oxygenation level-dependent (BOLD) response may be absent, attenuated, delayed or even reversed in the pathological vessels of high-grade brain tumors or arteriovenous malformations (AVM) lacking the normal vascular autoregulation so that the hemodynamic response function (HRF) dissociates from underlying patterns of neural activity (neurovascular “uncoupling”; [4, 25, 38]). Similarly, fractional anisotropy (FA) and fibre traceability are generally reduced by perifocal tumor edema and the signal loss of high-flow AVMs or cavernous malformations - regardless of whether the fibres close to the lesion are destroyed or not. Furthermore, the “true” spatial extent and functional relevance of neuronal activations and fibre tracts cannot be established by fMRI and diffusion tractography. Both measure the fMRI and diffusion signal *in vivo* but do not, *per se*, involve iatrogenic reversible “lesioning” by narcotics (such as amobarbital), electrical or transcranial magnetic stimulation to predict what areas / tracts can be considered expendable or are, in fact, indispensible, for specific brain functions.

Studies prior to the implantation of cochlear (CI), auditory brainstem (ABI) or midbrain (AMI) devices, on the other hand, promise to inform the clinician if such surgical implantation may be effective to restore hearing, at what level the implant should be placed (CI: inner ear, ABI: lower brainstem or AMI: midbrain) and on which side (e.g., which ear should host the CI). fMRI and tractography for these purposes are technically demanding and have only been adopted by a few specialized centres. fMRI prior to CI involves noninvasive extra- or invasive transtympanic promontory testing. Both require MR-compatible stimulation equipments which have been developed for investigative use [4, 6]. Additionally, fMRI audiometry can be performed by read-out omissions from echo-planar imaging (EPI; [5]) or active noise cancellation (ANC; [9, 12]) which is also useful to transmit auditory stimuli for clinical speech mapping, for example (cf. Fig. 4). Tractography of the entire ascending auditory pathway is quite difficult (due to its complex architecture with crossing and kissing fibres at the infra- and supratentorial level) but may supplement fMRI audiometry and promontory testing (Fig. 1; [11]).

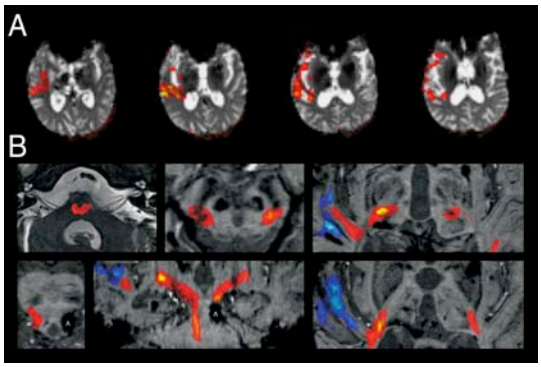

Fig. 1. (A) fMRI audiometry by read-out omissions from EPI (*red-to-yellow*) in a binaurally deaf traumatic brain injury (TBI) patient revealing right auditory activations only. (B) fMRI promontory testing of the left ear (*blue-to-lightblue*) confirming right auditory activations only. Probabilistic tractography of auditory pathways (*red-to-yellow*) detecting the underlying disruption of the upper left lateral leminiscus and inferior colliculus by an axonal shearing injury and bleed (^). It was concluded that the left ear should host the cochlear implant. The patient was successfully implanted.

Over the past decade, clinical fMRI and tractography have not kept up with the extent or technical sophistication of non- and preclinical scientific applications of the very same methods. Presurgical tractography, for example, often continues to rely on 6 or 12 diffusion directions only even though it has been demonstrated that at least 30 unique sampling orientations are required for a robust estimation of diffusion tensor orientations [27]. Current draft guidelines of the ACFNR (2012; [2]) do not specify a firm minimum of unique diffusion encoding directions for clinical diffusion tensor imaging and tractography nor recommend a set of most sensitive pre- and postprocessing algorithms to be used. In general, clinical settings favour speed regardless of accuracy for data acquisition and analysis. Clinicians often lack a basic understanding for the methodological advances, data acquisition, pre- / postprocessing and computing requirements as well as their respective benefits in fMRI and tractography applications. In this regard, both methods seem fashionable just by virtue of the colored brain images they provide. Very few neurosurgeons and neuroradiologists appreciate the specific demands, limitations and utility of fMRI and tractography for clinical purposes. That is why representatives of both specialities tend to be either overly enthusiastic or critical with respect to the application of these methods. Most clinicians actually expect fMRI and tractography results to be computed and ready for transfer into the neuronavigation system once the patient leaves the scanner. This is clearly not the case and would sacrifice taking advantage of most advanced data analysis strategies for which no ready-made solutions are available. Similarly, the majority of clinicians do not recognize the necessity of detailed neurological and neuropsychological examinations *prior* to conducting any fMRI exam, in particular. Current Procedural Terminology (CPT) codes of the AMA for clinical fMRI [22] have pointed to the importance of neurofunctional test selection and administration by physicians or licensed clinical psychologists. However, the practice guidelines for fMRI of the ACR (2007; [1]), issued the same year, make no reference to neuropsychological testing prior to conducting fMRI exams. Despite the CPT codes, fMRI and tractography are generally not adequately (or specifically) reimbursed for. It seems easier to obtain grant money for preclinical scientific projects on large subject samples than for highly individualized applications to optimize clinical decision-making that translate the advances of the former into medical practice. Although it constitutes an essential prerequisite to successful and effective clinical application, patients and fMRI paradigms remain poorly characterized and selected. Patients feel less at ease than controls with scanning, move more and often present with neurological or cognitive deficits. Paradigms to localize specific parts of the speech eloquent cortex should, for example, bypass unspecific visual or auditory processing deficits but target specific yet possibly subtle language deficits of the patient under examination. This requires careful and dedicated examination by a board-certified neuropsychologist. Mode and speed of stimulation (including task vs. rest cycling frequency) should be adjusted to the patient’s individual performance level. It makes no sense, for example, to expose a patient with a left parietal lesion and impaired visual attention to a visual language paradigm the patient cannot follow or keep up with (cf. [4]). Unfortunately, letter-cued word generation continues to be widely used for speech mapping although it is largely just a fluency and not really a good language task. Complex brain functions - like modular speech and language, reading and writing abilities - cannot be mapped, if at all, by a single paradigm [33]. Often multiple runs and different paradigms are needed. Clearly, more research needs to be done to design appropriate paradigms for patients subjected to presurgical fMRI depending on their type and level of impairment. Block designs continue to prevail over event-related and mixed designs for clinical fMRI. Optimal epoch lengths, which are in the order of 12 to 18 secs based on the canonical HRF, may be shorter for modelling transient responses of the auditory system [20], for example, and longer to evoke and capture complex brain functions like speech and language.

Resting-state fMRI (RS-fMRI) is beginning to be explored for its clinical utility [29, 31]. It may be used to detect resting-state networks (RSNs) and intratumoral (de-)activations even in patients who are not able to perform and comply with specific tasks. However, the presurgical relevance of RS-fMRI is limited. The robustly detected sensorimotor and visual RSNs can, for example, in most cases be delineated by pure anatomic criteria. Here, RS-fMRI may only be useful in space-occupying lesions with profound mass effect obscuring the central sulcus or calcarine fissure. Contrary to other claims [29], RS-fMRI is not well suited to map speech and language functions because these crucially depend on specific tasks. RS-fMRI of "inner" speech and language functions relies on circular assumptions of spatial network localization, which may overlap with other (such as working memory and executive) cognitive functions, while we consider the temporal correlation with an external validator (i.e., the time-course of the paradigm to map speech and language) necessary in this particular case. The reasoning will be further explained in the talk. RS-fMRI has also been combined with EEG recordings in the scanner to localize the source of pathological interictal (and / or ictal) discharges but the utility and predictive value remains controversial [4].

In terms of the data acquisition, multiband-accelerated EPI (MB-EPI) recordings enable unprecedented increases in temporal resolution, shortening of acquisition times and also higher spatial image resolution for both fMRI and diffusion tractography [17, 35, 37]. MB-EPI has not yet been systematically applied to clinical fMRI and tractography. After extensive testing, we now use it to sample 160 unique diffusion directions at an isotropic image resolution of $1.8mm^3$ in less than 10 min. Increased EPI image resolution can also, along with appropriate corrections for geometric image distortions, improve the registration to structural high-resolution images fed into the neuronavigation systems. Given that the thermal noise contribution increases at higher image resolutions, spatial smoothing of fMRI time-series preprocessing needs to be maintained at approximately similar FWHM values (i.e., increased relative to the voxel size) to achieve comparable contrast-to-noise ratios and to detect activations at a similar sensitivity [21]. MB-EPI may, in the near future, also be combined with k-space density weighted EPI to improve spatial and temporal signal-to-noise ratios for clinical applications (SNR; [41]). T2*-weighted BOLD-sensitive EPI continues to be most widely used for clinical fMRI. Arterial spin labelling (ASL) has not quite made it into the clinic despite the fact that it offers the opportunity to noninvasively study perfusion of brain tumors at rest [4], RSNs [30] and functional activations especially at low task frequencies [39]. Furthermore, local dephasing / signal loss (e.g., blooming in cavernomas) and geometric distortions tend to be less on ASL- than on BOLD-EPI which typically uses longer echo times (TE) and effective echo spacings (ESP). The relative lack of presurgical clinical ASL applications may be due to partial brain coverage of many ASL recordings. Additionally, the actual circulation time is often unknown and ASL sequences using multiple inversion times (TI; with or without dual TE to obtain additional BOLD contrast) for improved fitting are time-consuming to acquire.

Adequate distortion correction of EPI is crucial for clinical application of both fMRI and diffusion tractography. As yet, it has not been implemented by the vendors as an inline preprocessing step. Geometric EPI distortions can be reduced by lowering the effective ESP, e.g. through partial parallel image acquisitions, and corrected by collecting additional point spread function or field maps, or based on spin-echo (SE) EPIs at different phase-encodings [3, 37]. The latter has recently proven particularly effective - both in terms of the additional acquisition time required as well as the performance and handling of image intensities. In patients with previous surgery, craniofix and catheter devices such as Ommaya reservoirs, EPI can distort the underlying anatomy by 30 mm and more which needs to be corrected for and will be illustrated in the talk.

Analysis of clinical fMRI and tractography data should primarily minimize the risk of FNs (see above), i.e. employ the most sensitive strategies to detect neuronal activations and axonal fibre bundles. Making sure that the inclusion mask covers the pathological lesion of interest despite potential signal loss is essential [19]. Intra- and perilesional signal loss, e.g. due to intratumoral or cavernoma bleeding residuals, may escape intensity-based thresholds for mask generation. For clinical tractography, probabilistic methods tend to outperform the more widely used deterministic streamlining algorithms [11]. While the increased sensitivity of probabilistic tractography may entail false-positive (FP) detections of structural connections, these can – along with transformation into appropriate conditional path probabilities and subsequent thresholding – generally be reduced to acceptable presurgical tracking results. For clinical fMRI, we recommend to perform both model-based (according to the General Linear Model: GLM) as well as independent component analyses (ICA). ICA results can be correlated in the temporal domain (Tmode) with the model to select components of interest *post hoc*. In our experience, ICA tends to be more sensitive *and* specific than GLM results because of the ability of the ICA to reduce voxelwise variances and to separate motion and unspecific sensory (such as visual) components from the activation maps of interest (such as speech and language activations upon visual stimulation by reading nonfinal embedded clause sentences vs. consonant strings). FP fMRI activations can, among other reasons, result from stimulus-correlated motion [18] while FN results are, for example, associated with prior surgery [28]. Additionally, seed-based correlation analyses can be used but have rarely been applied to presurgical mappings. For statistical inference, both activation and deactivation maps should be inspected and considered. This is due to the fact that pathologically delayed or paradoxically inverted BOLD responses will show up as deactivations to the task [4, 6, 7, 8]. Thus, bidirectional (i.e., F-) testing is mandatory for clinical purposes. Thresholding of statistical maps from GLM- and ICA-based analyses should also primarily protect against FN results. This differs from the vast majority of non- and preclinical scientific applications where stringent FP protection (i.e., by correction for multiple comparisons and control of the family-wise error rate) is desired. Such standard thresholding is generally accomplished by testing the null hypothesis (H0) that no activation has occurred and accepts activations only where the H0 cannot be maintained, i.e. to strongly support true-positive (TP) findings. This approach is obviously not the best for presurgical mapping (or tracking) which strives to assert what gray matter areas (or white matter tracts) are not "eloquent", i.e. represent true-negative (TN) findings. Unfortunately, standard FP control continues to prevail in clinical fMRI. It assumes that no activation has occurred in, for example, a patient with a brain tumor in proximity to speech eloquent areas despite that fact that he successfully performed the task in the scanner. Alternative hypothesis (H1) testing by, for example, Gaussian Gamma Mixture Modeling (GGMM; cf. [4, 40]) explicitly models the tails of the distribution to detect relevant (de-)activations and thereby, at least theoretically, minimizes FN results. Recently, other statistical thresholding procedures, in part specifically tailored to presurgical application, have been developed and are now tested [15, 26, 36]. It has to be kept in mind, however, that it is very hard to convey the probabilistic nature of fMRI and tractography results to the neurosurgeon who has to make deterministic decisions about the surgical approach and extent of resection. In fact, the probabilistic nature of the spatial extent of fMRI activations and fibre pathways can be considered one of the main barriers to their further clinical adoption. After thresholding and spatial transformation into high-resolution structural space, fMRI (i.e. GLM plus selected ICA) and tractography results can be merged into a single or separate 4D files, maximum intensity projected along the 4^{th} dimension into a 3D file and rendered onto the anatomical (e.g., 3D T1-weighted post contrast or T2-weighted) MR image used for neuronavigation which usually needs to be (back-)converted into DICOM format to be fed into the neuronavigation system (Fig. 3(c)). These images can also be used to simulate the surgical access, resectability and extent of resection by "virtual neurosurgery" (Fig. 2). More rigorous research is needed to establish sensible guidelines for thresholding cutoffs in clinical fMRI and tractography. Also, the potentially serious issue of intra-operative brain shifts with respect to presurgical navigation data sets has not been solved satisfactorily. Due to the specific constraints of the operating room (OR), edema and bleedings due to surgical manipulation *in situ* and the necessary sedation of the patient, we consider this primarily a registration problem and do not advocate intra-operative fMRI or diffusion tractography [11].

The most important functions and fibre pathways to map and track prior to resective surgery are the following: Depending on the lesion localization, the mapping of speech and language functions primarily includes Broca's inferior frontal (F3), Wernicke's superior temporal (T/t1) and Geschwind's inferior parietal (P2) as well as Exner's middle frontal (F2) and Mills' basotemporal (or the visual word forming, T4) area. These cannot be localized by anatomic criteria alone. Tractography along the ventral and dorsal stream of speech and language [23] may reconstruct the arcuate fasciculus (AF; dorsal pathway; Fig. 2) and the inferior fronto-occipital fasciculus (IFO) together with fibres of the extreme capsule (EmC; ventral pathway; Fig. 3; [34]). The inferior longitudinal and Wernicke's perpendicular fasciculus may be essential for reading and their surgical damage may result in alexia without agraphia [10, 11]. Pyramidal tractography is essential for subcentral lesions [4], and tractography of the optic radiation may be useful for planning

anterior temporal lobectomies (ATLs). Given that the optic radiation extends as high as the superior temporal sulcus (t1), its tracking may be useful prior to surgery in more posterior lesions to avoid unnecessary visual field deficits [11]. Probabilistic tractography of white matter fibre bundles can be scripted using AutoPtx (part of FSL, http://fsl.fmrib.ox.ac.uk/fsl/), for example, which uses the FA image for standard space registration in order to (back-) transform predefined seed, target, exclusion and stop masks into subject space [13]. This is, according to our experience, relatively robust even in large brain tumors distorting the individual anatomy but needs to be confirmed for every case. Visual and motor mapping by fMRI are rarely indicated because the primary visual and motor (as well as the auditory) cortex can be located in the vast majority of cases by anatomic criteria. Nevertheless, motor mapping continues to be widely performed for no real medical reason (cf. [14]). Mapping the supplementary motor area (SMA) and memory functions are, despite the deficits that may occur upon surgical damage, controversial and seldom conducted. Deficits after damage to the SMA (like mutism) are usually transient, and verbal memory mapping is as well not considered strongly predictive (e.g., for ATL outcome; [32]). Mapping the auditory cortex is, aside from its straight anatomic definition, hardly ever performed prior to resective surgery because the resulting deficits are generally minor and well coped with. Mapping and tracking of auditory activations and fibre pathways prior to CI (and potentially ABI or AMI) have already been discussed above.

III. Validation and Outlook

Aside from their probabilistic nature and the time-consuming, computational and interdisciplinary demands of fMRI and tractography, which make it hard to integrate them into the clinical workflow, external validation and current impracticality to separate functionally essential from dispensable activations and tracts impose the main challenges to a more widespread use of these methods. Electrocortical and -subcortical stimulation monitoring (ESM) and Wada testing are generally considered gold standards for validation. However, the scope of neuro(psycho)logical testing during the Wada procedure and ESM in the OR is quite limited, must be well planned and cannot match or replace more detailed pre- and postoperative assessments. In fact, both procedures (Wada and ESM) are not standardized themselves and failures have been documented. The patient continues to be sedated during “awake craniotomies” (a misnomer when full anesthesia / sedation is used during trepanation), and effective Wada testing can be limited by premature sedation (especially due to rapid circulation / shunting such as in high-flow AVMs, for example). Furthermore, ESM evokes seizures in up to 15 % of the patients, approximately, and by far not every patient will tolerate and be eligible for such procedure. Most importantly, electrocortical and -subcortical stimulation is not punctually selective but spread over up to 2 cm across the cortex and into the neighbouring brain tissue. According to appropriately published data and our own experience, the correspondence of ESM with presurgical fMRI and tractography results is generally good and within this range. Hopefully, the better the functional anatomical knowledge of the neuroradiologist and the more qualified presurgical fMRI / tractography are conducted, including a meticulous clinical examination, the more patients can be spared from intricacies of ESM and Wada testing at no cost of persistent postoperative functional deficits. At least, fMRI and tractography can inform ESM to limit the number of relevant stimulation sites. Notably, combining fMRI and tractography may be able to substantiate the functional relevance of a given tract: If the structural connectivity distribution between two regions A and B predicts their functional activation pattern on the surface, then this increases the confidence that the given tract that connects A and B is indeed involved in generating the activations and is thus functionally relevant [24]. This approach may be used to assure cerebral dominance for speech and language functions, for example (Fig. 4), which has traditionally been assessed by Wada testing prior to epilepsy surgery. Cerebral dominance is notoriously difficult to confirm using fMRI alone because activations tend to occur bilaterally and even spatially less extensive activations on one hemisphere may be crucial for task performance. Mapping the correspondence of fMRI activation and structural connectivity probabilities (Fig. 4) could, in the future, be used to add further evidence to the functional involvement of specific fibre tracts and to establish interhemispheric dominance for clinical purposes.

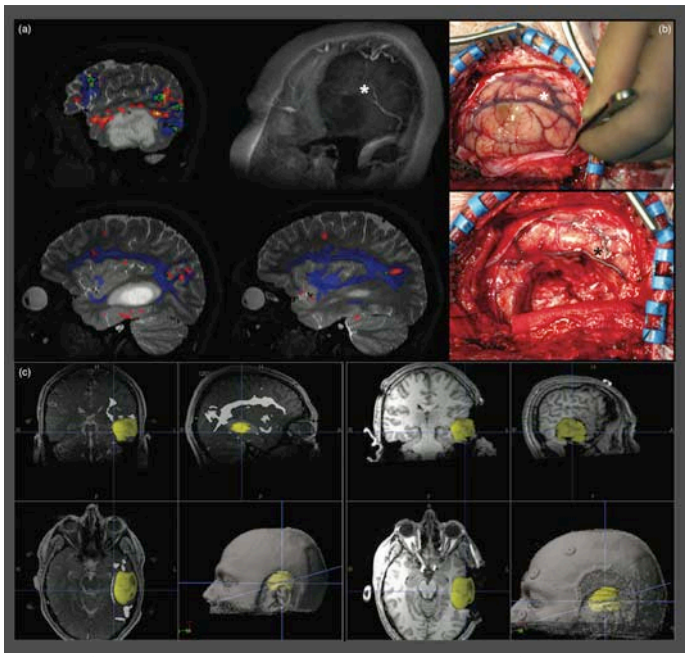

Fig. 3. (a) fMRI activations (*red-to-yellow*; evoked by reading nonfinal embedded clause sentences) and probabilistic tractography with crossing fibres modeling (*blue-to-lightblue*) of dorsal (AF) and ventral (IFO / EmC) pathways of speech and language in a patient with a grade III astrocytoma in the lower left temporal lobe centered on the middle to inferior temporal gyrus (T2/3) just below Labbé’s vein (*). (b) Labbé’s vein guided the surgical resection as a landmark in the intra-operative situs. (c) Intra-operative neuronavigation before (left lower four panels) and after the resection (right lower four panels, updated by an intra-operative MRI scan). Note that there was no significant brain shift. Resection of the tumor (*yellow*) was gross-total but limited by its proximity to the IFO. After surgery the patient exhibited no visual field defect but some semantic speech and language impairments and, probably due to affection of Wernicke’s perpendicular fasciculus, ‘pre-angular’ pure alexia without agraphia. He could, for example, not tell the meaning of ‘No ifs, ands, or buts!’ nor read any SMS but was able to type text messages. Both deficits completely resolved over the course of 2 months.

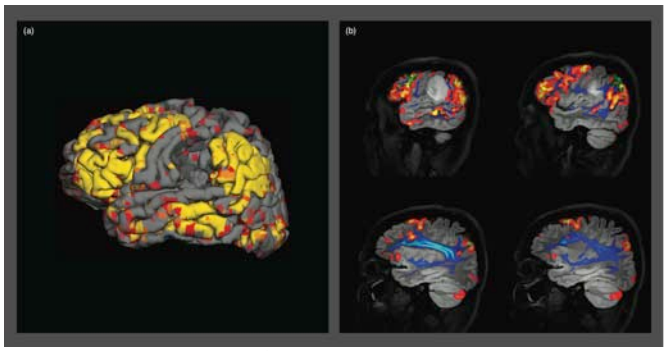

Fig. 2. (a) Virtual neurosurgery: fMRI activations (*red-to-yellow*; evoked by reading nonfinal embedded clause sentences) and (b) probabilistic tractography with crossing fibres modeling (*blue-to-lightblue*) of the dorsal (AF) and ventral (IFO / EmC) pathways of speech and language in a patient with a grade III astrocytoma in the lower left parietal lobe, centered on the supramarginal gyrus (P2). As confirmed during “awake craniotomy”, resection was limited by the proximity and presumed infiltration of the AF (top right image). Postoperatively, the patient developed signs of classical conduction aphasia with profound difficulties in repeating tongue twisters which completely resolved over a period of 3 months.

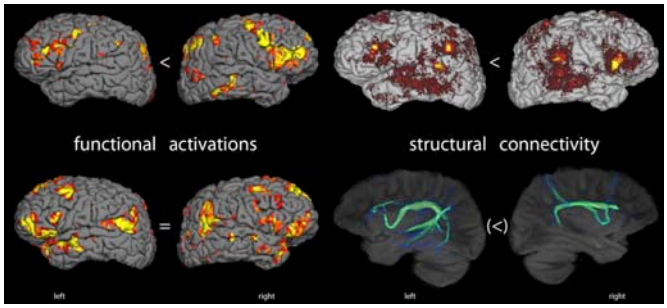

Fig. 4. fMRI activations (*red-to-yellow*; evoked by auditory description-cued naming under ANC of EPI noise) in a 12-year-old left-handed boy with intractable left frontotemporal seizures of a nonlesional epilepsy examined for language lateralization (left panel). ICA revealed two components significantly correlated with the speech paradigm: one right-lateralized component of the dorsal stream (top) and another bilaterally represented component of the ventral stream (bottom). Probabilistic tractography with crossing fibres modeling demonstrated a hypoplastic anterior segment of the left AF (right lower panel). Surface correspondence of fMRI activation and structural connectivity probabilities (right upper panel) was stronger on the right, supporting Broca’s unusual right dominance prior to invasive EEG recordings.

IV. Key Points

The preoperative neurological and neuropsychological condition of the patient is the best indicator of what to map and track, how to map it and what functional risks opposing the benefits will be associated with the surgery. In epilepsy surgery (ATL, in particular) patients with no preoperative deficit and normal structural MRI are at the highest risk to develop new postoperative deficits while in resective surgery of brain tumors and other intra-axial lesions patients with no preoperative deficits will tend to fare best.

Brain functions that are invariably tied to anatomically identifiable brain areas ("absolute representation" in the primary motor, visual and auditory cortex) rarely require any mapping. However, fMRI audiometry and promontory testing can assist the evaluation of CI (and ABI or AMI) candidates and, potentially supplemented by tractography of auditory projection pathways, guide the decision on what side (and level) should host such implant device. Pyramidal tractography, on the other hand, is essential for sub-Rolandic lesions.

Brain functions of variable anatomical localization and extension may benefit from mapping prior to resective surgery. Supplementary motor, speech and language functions are of such "relative representation" (according to Exner [16], cf. [11]). Because SMA syndromes upon unilateral SMA damage are, in the vast majority of cases, transient, it is primarily speech and language that the combination of fMRI, tractography and subsequent intra-operative neuronavigation may be useful to preserve. Their results can successfully be used for choosing the best surgical approach, to limit the relevant ESM sites and possibly the extent of resection. The major obstacles for further and more widespread clinical application of these methods are related to the inherent risk of FN results as well as FP detections in the sense that functionally dispensable fMRI activations and fibre pathways can currently not be separated from essential blobs of activation and tracts.

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