

Relationships between essential cortical language sites and subcortical pathways

Clinical article

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Object. Maps produced using either electrical stimulation or functional imaging have demonstrated a distributed network of cortical regions involved in expressive and receptive language tasks. The pattern of connectivity among components of this network has begun to be explored with diffusion tensor (DT) imaging, but has yet to be completely characterized. In this study the authors used DT imaging-based tractography to examine the interrelationship between cortical areas found to be essential for language by intraoperative electrical stimulation.

Methods. The authors localized the arcuate fasciculus (AF), a white matter fiber system connecting frontal and parietotemporal areas in 10 patients, 9 of whom subsequently underwent left hemispheric language mapping.

Results. The authors found that 81 (79%) of 102 essential language sites (ELSs) were closely related to the AF. Of all ELSs, 59% were located within 7.5 mm of AF fiber pathway terminations, and another 20% contained pathways terminating closer to the AF than would be expected by chance ($p < 0.05$). Additionally, direct subcortical stimulation of the AF following focal cerebral resections produced transient language deficits. The close spatial relationship found between ELSs and the AF suggests that tractography data alone may be used for localization of ELSs.

Conclusions. The deficits evoked by subcortical stimulation validate and demonstrate the utility of this AF localization technique, and provide further evidence that the AF is an important pathway for fluent language. Taken together, these results demonstrate that DT imaging of the AF may be used to predict the location of brain areas that will be eloquent by the standards of stimulation mapping. (DOI: 10.3171/2009.3.JNS081427)

KEY WORDS • diffusion tensor imaging • arcuate fasciculus • language • Broca area • intraoperative stimulation mapping • inferior longitudinal fasciculus • uncinate fasciculus • superior longitudinal fasciculus

THE fluent comprehension and production of language is predicated on the rapid transmission of information between a distributed set of brain areas shown by functional imaging³³ and lesion studies^{20,21,32,45} to make up the language network. Although a growing body of research in which DT imaging is used has begun to provide information about how long-range white matter fiber tracts may connect language regions,^{13,22,24,27,34,37,48,50,51,64} the connectivity pattern of this network remains to be fully documented.

Patients with tumors or epileptic seizure foci in the

dominant hemisphere present a unique opportunity to evaluate functional and structural relationships of the cortical and subcortical substrates of the language system. In many of these patients, cortical language sites are identified by electrical cortical stimulation (using CSM)⁴⁶ during the performance of various language tasks. Areas in which language function is disrupted can then be related to preoperative functional and structural imaging data.

In the present study, we asked how cortical ELSs as localized by CSM are related to a major subcortical white matter language pathway, the AF, as localized by DT imaging-based tractography. This technique allows white matter tracts to be examined *in vivo*^{8,15,42} by computing the principal direction of water diffusivity at each imaging voxel, and reconstructing fiber pathways that represent bundles of many axons by tracking the largest magnitude direction component in 3 dimensions.

Abbreviations used in this paper: AF = arcuate fasciculus; CSM = cortical stimulation mapping; DT = diffusion tensor; ELS = essential language site; FA = fractional anisotropy; fMR = functional MR; NIH = National Institutes of Health; sCSM = subcortical CSM; SMA = supplementary motor area; VOI = volume of interest.

Large cortical association fiber tracts appear to be reliably identified by this method, with their origin, course, and terminations consistent with postmortem neuroanatomical studies.⁴⁰ The AF is arguably the most significant white matter fiber tract relevant to language function,^{11,19,54,62} even though there is some debate over the precise functional deficit that may accompany damage to the AF.^{1,6,39,58,65} The AF is considered part of the superior longitudinal fasciculus,^{13,37,55} and converging lines of evidence support the idea that this pathway connects frontal cortical areas important for speech production (that is, the Broca area) with temporal and parietal cortical areas important for language comprehension.^{21,56} Therefore, we hypothesize that a close relationship between ELS and AF terminations must exist, and our principal aim here is to quantify that relationship by using DT imaging–based tractography. Establishing the ELS-AF relationship may have important clinical implications, because the location of essential language areas could be predicted based on terminations of specific long-range subcortical pathways. Additionally, it may advance our understanding of language organization in the human brain: is the AF structurally arranged such that it could mediate connectivity between most essential language areas, as had been hypothesized by Wernicke and Geschwind? Or, does the AF connect only a small proportion of language sites, with other subcortical pathways mediating information transmission to support language?

A secondary, exploratory objective of the present study was to assess the effect of stimulation of the AF on language function. This was accomplished by direct subcortical stimulation in a subset of patients in whom focal cerebral resections allowed exposure and stimulation of white matter constituting AF fiber pathways. Language deficits induced by subcortical stimulation of the AF provided 2 important pieces of information. First, they guided the refinement of hypotheses about how this structure supports specific aspects of language function, and second they validated the utility of DT imaging–based tractography for identifying and preserving subcortical language pathways during neurosurgical interventions.

Methods

Patient Population

Ten patients (5 of each sex, 1 left-handed and the rest right-handed, mean age 40.9 ± 12.5 years [mean \pm SD]) who were scheduled for awake craniotomy and focal cerebral resections were enrolled. Written informed consent was obtained in accordance with the policies of the University of Texas Committee for the Protection of Human Subjects. Handedness was assessed in all cases (Edinburgh Handedness Inventory).⁴⁷ No patient had gross language deficits before surgery, and this was confirmed by extensive neuropsychological evaluation in 5 of the patients. All patients had left hemisphere language dominance determined by fMRI imaging. This was corroborated in 1 patient (Case 1) by a Wada test. Nine patients underwent left hemisphere cortical stimulation during awake mapping. One (Case 6; left-handed) underwent awake right hemisphere cortical

stimulation prior to resection of a parietal lobe tumor. Patient characteristics are summarized in Table 1. As part of the resection, 6 of the 10 patients underwent sCSM, 5 in the left hemisphere and 1 (Case 6) in the right (nondominant) hemisphere. Except for 1 patient (Case 2, a native Spanish speaker who spoke fluent English), all others were native English speakers. Language mapping in both the MR unit and in the operating room was performed in English.

Image Acquisition and Processing

Participants underwent neuroimaging, for which a 3-T MR scanner (Philips Medical Systems) equipped with an 8-channel SENSE head coil was used. Anatomical images were collected using a magnetization-prepared 180° radiofrequency pulse and rapid gradient-echo sequence optimized for gray/white matter contrast with 1-mm-thick sagittal slices and an in-plane resolution of 0.938×0.938 mm. Diffusion-weighted images were collected with the Philips 32-direction diffusion encoding scheme (high angular resolution) with the gradient overplus option. Seventy axial slices were acquired with a 224×224 field of view (1.75×1.75 -mm pixels), 2-mm slice thickness, and a maximum b-value of 800 second/mm².

The anatomical MR image for each patient was used to construct mesh models of the gray/white matter interface and pial surface.¹⁷ Image realignment, computation of the diffusion tensor, and spatial transformations were performed using AFNI programs.¹⁶ For each patient, individual diffusion-weighted image volumes were realigned to the subject's skull-stripped anatomical MR image. A single-model diffusion tensor was computed from the realigned diffusion-weighted volumes. An affine transformation (12 parameters: shifts, rotations, scaling, shearing) of each patient's skull-stripped anatomical MR imaging to the T1-weighted Montreal Neurological Institute single-subject template¹⁴ was computed.

Tractography and AF Identification

An FA value was computed at each voxel from the normalized variance of the eigenvalues of each diffusion tensor. Deterministic fiber tracking was performed with DTIQuery v1.1 by using the streamline tracking algorithm.^{2,57} A constant step size of 4 mm, an FA termination threshold of 0.15, and an angular threshold of 45° were used to generate a set of whole-brain fiber pathways.

For each patient, the inverse of the affine transform matrix relating each individual's anatomical MR imaging to standard Montreal Neurological Institute space was used to generate a mask in native coordinate space that included voxels labeled Brodmann areas 44 and 45. Specifically, maximum probability maps from the SPM Anatomy Toolbox programs²³ representing Brodmann areas 44 and 45, cytoarchitectonic areas implicated in language function,^{3–5} were binarized, transformed from standard to native space by using the inverse transform, and conjoined to create a single binary mask. To account for coregistration errors, the mask was dilated medially by 2 voxels toward the white/gray matter border. Identification of AF fibers was performed automatically by using functions written

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TABLE 1: Characteristics in 10 patients who underwent CSM*

Case No.	Age (yrs), Sex	Handedness	Diagnosis	sCSM
1	18, F	rt	lt temporal lobe epilepsy	no
2	44, F	rt	lt precentral gyrus tumor	no
3	42, F	rt	lt temporoparietal cavernous malformation	yes
4	51, M	rt	lt postcentral gyrus tumor	yes
5	40, F	rt	lt insular tumor	no
6	41, M	lt	rt parietal tumor	yes
7	20, M	rt	lt anterior frontal lobe epilepsy	yes
8	55, F	rt	lt frontal lobe tumor	yes
9	47, M	rt	lt frontal lobe tumor	yes
10	51, M	rt	lt temporal lobe tumor	no

* The hemisphere and location of the pathological entity are listed under diagnosis. All 10 patients underwent CSM, and the subset who underwent sCSM is indicated.

in Matlab 7.4 (Mathworks), which was used to evaluate whether each fiber pathway intersected with the left or right binary mask. All intersecting fibers in each hemisphere were saved for display and analysis. Fiber pathways from multiple brain areas intersected with the Broca area, but only fibers passing posteriorly from the Broca area through a region including the white matter bundle superolateral to the insula⁴¹ were eligible to be considered as part of the AF. This method of identifying the AF is essentially a 2-VOI approach;¹² the VOIs consist of the Broca area and a small area of white matter superior to the insula. This isolates both the long direct segment connecting the Broca area to the Wernicke area as well as the anterior indirect segment connecting the Broca area to the Geschwind territory.¹³ To ensure accuracy, each patient's AF was inspected by interactively changing the size and shape of the 2 VOIs to make sure that no fiber pathways belonging to the AF were excluded. Additionally, because some patients had mass lesions, the accuracy of the Broca area mask was verified by examining its spatial outline on cortical reconstructions. Masks for all patients included the opercular (Brodmann area 44) and triangular (Brodmann area 45) segments of the inferior frontal gyrus and some portion of the precentral gyrus (Brodmann area 6).

Neuronavigation and Awake Stimulation Mapping

A T1-weighted anatomical MR image with the AF fibers superimposed as white voxels was loaded as an Analyze format volume (AnalyzeDirect, Inc.) onto a Stealth workstation for intraoperative navigation, after registration of the patient's head position to the image volume by using scalp-based fiducials (Medtronic Navigation).

Awake mapping was performed using well-established methods, which are characterized in detail elsewhere.²⁶ Briefly, patients were deeply sedated with intravenously administered dexmedetomidine and remifentanil, after which a laryngeal mask airway was placed. After immobilization of the skull, a field block of the planned surgical site was accomplished with local infiltration of a combination of bupivacaine and lidocaine, and the

craniotomy was performed. The intravenous anesthetic agents were stopped, the patient awoke, and the laryngeal mask airway was removed.²⁵

Language testing comprised visual naming (Boston Naming Test³⁵), repetition of auditory phrases, and naming of objects described in the auditory domain.²⁸ Table 2 summarizes the tasks used to assess language, the deficits evoked by stimulation, and the timing of stimulation relative to either the encoding (that is, listening to a phrase before being asked to repeat the phrase) or the production phase of a task (speaking a phrase after listening to it). The CSM was performed using 3- to 5-second trains of 500 msec biphasic pulses between 1 and 10 mA in amplitude delivered at 50 Hz by using an Ojemann stimulator (Integra Neurosciences) during stimulus encoding (picture viewing or auditory phrase presentation), or during articulation. Stimulation was delivered at cortical surface points ~ 5 mm apart. Concurrent electrocorticography was performed to monitor for afterdischarges. Prior to mapping, afterdischarge thresholds were established^{36,49} and the maximum current that could be safely applied without triggering afterdischarges was used for CSM.

The sCSM was performed after resection of cortex in 6 cases by using current amplitudes between 3.5 and 9 mA. In 5 of these cases, the area of resection exposed white matter such that the stimulation probe was able to be targeted toward identified AF fiber pathways. During sCSM, patients were engaged in auditory naming, visual confrontation naming, and in self-generated articulation (counting, reciting nursery rhymes or the alphabet). Locations of the sCSM sites were determined using concurrent frameless stereotaxy on the Stealth workstation. Because nonlinear brain deformation occurs during a craniotomy and following a cerebral resection,²⁹ some degree of error was present between the presurgical AF location and the stimulation electrode during surgery. In this investigation, no attempt was made to quantify the degree of shift precisely, and therefore all that can be stated with certainty is that we stimulated white matter in or in close proximity to the AF.

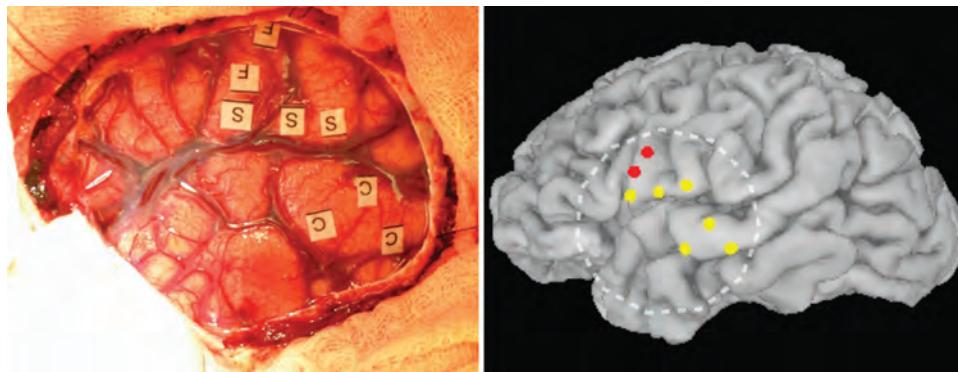


Fig. 1. Intraoperative photograph and 3D reconstruction showing localization of stimulation sites on cortical surface models. Each cortical stimulation site was assigned a 3D coordinate on the patient's reconstructed cortical surface by close estimation of its position relative to sulcal and gyral landmarks, based on intraoperative photographs. An example from one patient shows an intraoperative photograph of exposed lateral frontal and temporal cortex (left) with labeled language sites on either side of the sylvian fissure. Language sites are approximated by *colored spheres* on a cortical surface model (right); the *dashed line* represents the approximate boundaries of the craniotomy. See Table 2 for definitions of labels on brain surface.

Identification of Fiber Pathways Near Cortical Stimulation Sites

The ELSs were defined by a 3D coordinate identified in SUMA⁷ by using the mesh model of the cortical surface. Intraoperative photographs of labeled CSM sites were used to confirm the locations (see for example Fig. 1) of CSM coordinate centers because nonlinear brain deformation may have occurred during the craniotomy. Based on prior estimates of current spread in cortex,^{44,53,60,61} VOIs with 7.5-mm radii were placed around each CSM site. Because each CSM site was localized on gray matter but tractography pathways terminate in white matter, each ELS was displaced medially by 10 mm to ensure that it encompassed the gray/white matter border.

Statistical Assessment of Fiber Pathway Distance Relationships

The CSM regions were classified 2 ways. If any AF fiber terminations were contained within the VOIs as detailed above, this site was classified as having a direct relationship to the AF. If no AF fiber terminations were contained within the 7.5-mm-radius VOI around the ELS, all fiber pathways at that site were evaluated for an indirect relationship to the AF fibers. A bootstrapping method was used to evaluate whether any of the fiber pathways within these regions (hereafter called the ELS region fibers) had terminations at either end that were closer to AF fiber pathway terminations than would be expected by random chance. In other words, ELS region fibers (which may include corticocortical U fibers or other long-range-association fibers, or some combination of each) were evaluated for the proximity of their terminations to AF fiber terminations.

Specifically for each patient, a random surface node was chosen from the mapped hemisphere, displaced medially by 10 mm, and all fiber pathways with terminations within a radius of 7.5 mm were evaluated to determine if any was a member of the set of previously identified AF fiber pathways. If none was, the Euclidean distances between fiber terminations from each ELS and each AF fiber termination were computed to give an "m-by-n" distance matrix,

where "m" is the number of fiber terminations in the given ELS region and "n" is the number of fiber pathway terminations for the set of AF fiber pathway terminations. The mean and minimum values of this distance matrix were stored, and the process was repeated 10,000 times in each patient to build mean and minimum value null probability distributions. The mean value represents the proximity of ELS region fiber terminations to the whole set of AF fiber terminations, and the minimum value is the distance between the closest ELS region fiber termination and the set of AF fiber pathway terminations. In each patient, the distance matrix was computed for each set of ELS region fiber pathways, and the mean and minimum values were compared with the null probability distributions determined from Monte Carlo simulations. If either the mean or minimum value was found to occur with a probability of < 5% occurrence in the null distribution, that site was considered to contain at least 1 fiber with a termination proximate to an identified AF fiber termination that was closer than would be expected by chance. Stimulation of a cortical region with an indirect relationship to an AF termination site could be expected to excite indirectly a neural population connected with the AF proper.

Results

Identification of AF

The AF was identified from tractography data in each of the 10 patients. The AF pathways for each of the 9 patients who received left-hemisphere CSM are displayed in green in a sagittal view, with the FA volume as a background in Fig. 2. The presence of mass lesions (a cavernous angioma in Case 3, Fig. 2c; and a temporal lobe tumor in Case 10, Fig. 2i) altered the trajectory of the AF's posterior projections in 2 patients. A large frontal lobe tumor (Case 9, Fig. 2h) displaced the trajectory of several of the AF pathways. In all of these 3 cases the AF could be localized, and its terminations at either end could be visualized.

The CSM Sites Essential for Language

A total of 102 essential cortical language sites were

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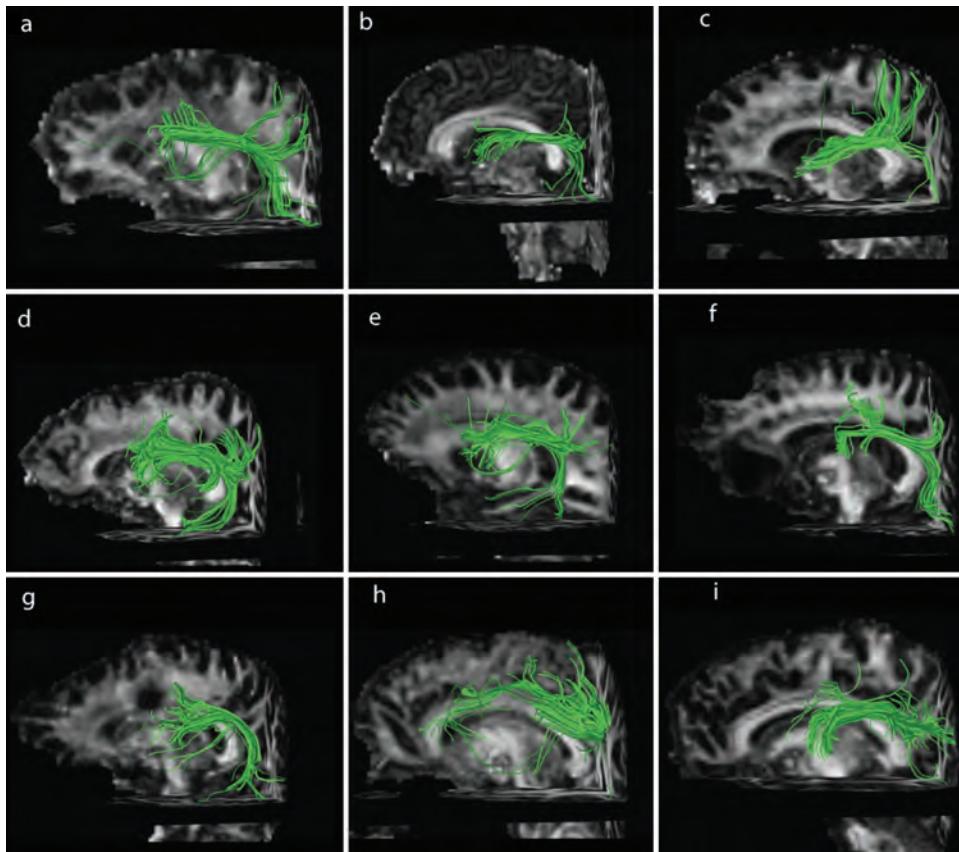


Fig. 2. Sagittal views of the left hemisphere demonstrating AF tractography pathways (green) overlaid on the FA volume of each of the 9 patients (a–i) who underwent dominant-hemisphere CSM.

found in the 9 patients who underwent left-hemisphere CSM. These sites are displayed as white spheres on each patient's reconstructed cortical surface anatomy (Fig. 3). Of the 102 cortical sites, a total of 36 were classified as essential for expressive language function—defined as a site where a deficit could be reliably evoked when stimulation was delivered during the production phase of the task ($S = 15$, $A = 8$, $R = 13$; see Table 2 for definitions of labels). A total of 38 sites were classified as essential for receptive language function—defined as a site where a deficit could be reliably evoked when stimulation was delivered during the encoding phase of the task ($N = 17$, $C = 21$). A total of 28 sites were classified as essential for both expressive and receptive language ($L = 28$). At these sites, separate stimulation during both the encoding and production phases of auditory naming and auditory repetition tasks disrupted function.

Direct Relationship Between CSM Language Sites and the AF

A summary of the relationship between the 102 ELS and AF pathways (Table 3) reveals that the majority of essential language sites (58.8%) had a direct relationship to the AF, defined as a positive CSM site with AF pathway terminations located within the immediate region (radius = 7.5 mm). Cortical stimulation delivered at these sites has the greatest chance of affecting some of the neuronal population contributing/connected to the AF or some AF axons directly. An example (Case 4) of multiple language

CSM sites with direct connectivity to the identified AF fibers is shown in Fig. 4.

Indirect Relationship Between CSM Language Sites and the AF

Of the 42 ELSs without a direct relationship to the AF terminations, it was found that 21 had an indirect relationship to the AF. These sites had fiber pathways with 1 end within an immediate region (radius = 7.5 mm) whose other termination points were closer to the terminations of the AF pathways than would be expected by chance ($p < 0.05$), as determined by a bootstrapping method. Stimulation at these sites would probably affect the neurons at AF termination sites by way of an indirect corticocortical route. An example of a CSM language site with indirect AF connectivity (Case 10) is shown in Fig. 5. The CSM of a site located on the superior temporal gyrus elicited both expressive and receptive language deficits, but none of the adjacent fiber pathways (shown in blue) were included in the set of identified AF fiber pathways (shown in green). Instead, the adjacent fiber pathways include several corticocortical "U" pathways, many of which terminate in proximity to posterior AF terminations.

Relationship Between CSM Language Sites and Other Subcortical Pathways

Tractography pathways near 21 cortical stimulation sites that had neither a direct nor indirect relationship to

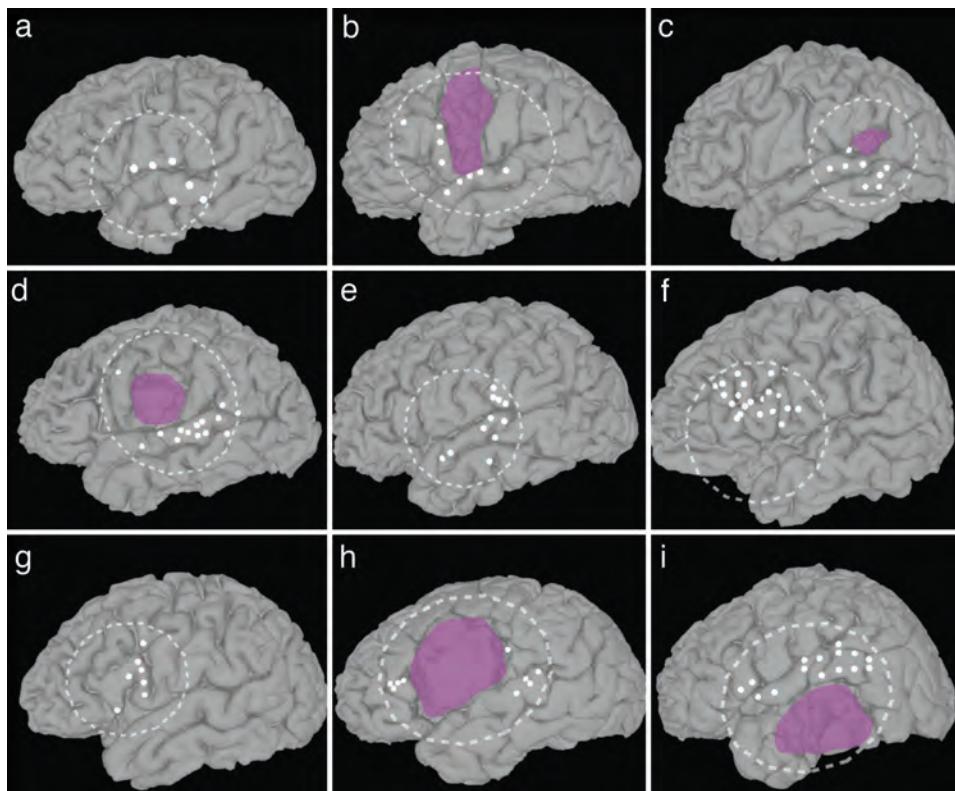


Fig. 3. Three-dimensional reconstructions revealing essential cortical language sites that were determined based on awake stimulation mapping. A total of 102 essential cortical language sites (white spheres) in the 9 patients (a–i) who underwent dominant-hemisphere mapping are displayed on each patient's reconstructed surface anatomy. Sites at which stimulation produced purely motor or sensory deficits are not depicted. The dashed lines represent the approximate boundaries of the craniotomy, and purple regions indicate the location of tumors or malformations that prevented accurate surface reconstruction.

the AF were identified. Five sites in 3 different patients (Cases 1, 4, and 5) were related to the inferior longitudinal fasciculus. Another patient (Case 8) had an anterior temporal lobe site that included the uncinate fasciculus. Ten sites in the patient in Case 7 located in the anterior frontal lobe were near pathways connecting lateral and medial frontal cortex (SMA/pre-SMA). The patient in Case 2 had a site in the anterior Broca area, with pathways passing to the dorsolateral prefrontal cortex. The

remaining sites included corticocortical pathways near the posterior terminations of the AF (Case 3), and a set of pathways that may actually be AF pathways, but whose trajectory through white matter was displaced medially by a large tumor (Case 9).

Subcortical Stimulation

After CSM and during resection of the tumor or epi-

TABLE 2: Language deficits evoked by electrical stimulation*

Type of Language Deficit	Description of Task Used to Assess Language Deficit	Timing of Electrical Stimulation
S, speech arrest	no comprehensible speech while counting &/or reciting the alphabet	during speech production phase
A, articulation	dysfluent but partly comprehensible speech while counting &/or reciting the alphabet	during speech production phase
N, naming	inability to name pictures of common objects	during picture presentation
R, repetition	inability to repeat auditorily presented phrases & sentences	during production phase
C, comprehension	inability to generate names from auditory descriptions or repeat auditorily presented phrases & sentences	during encoding phase
L, encoding & comprehension	inability to generate names from auditory descriptions or repeat auditorily presented phrases & sentences (C + R)	separately during production & encoding phases

* The type of deficit evoked by stimulation is listed, along with a description of the task used to assess the deficit, and the timing of stimulation in relation to the encoding or production phase of the language task. Expressive language deficits include "S," "A," and "R," because function is impaired when stimulation occurs during the production (that is, speaking) phase of the task. Receptive language deficits include "N" and "C" because function is impaired when stimulation occurs during the encoding (that is, viewing or listening) phase of the task. The label "L" includes sites where stimulation is given separately during encoding and production phases, and function is impaired in both.

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TABLE 3: Essential cortical language sites and their relationship to the AF*

Relationship to AF	No. of Sites (% of total)	No. of Sites/Patient†
direct	60 (58.8)	6.6 ± 4.6
indirect	21 (20.6)	2.3 ± 2.4
no relationship	21 (20.6)	2.3 ± 3.0
total	102	11.3 ± 4.4

* Each cortical stimulation site was found to have either a direct, indirect, or no relationship to the identified AF pathway terminations (direct) or the proximity of the terminations of pathways in the nearby region to the AF pathway terminations (indirect). The majority of ELSs (81 of 102) had either a direct or indirect relationship to the AF.

† Expressed as the mean ± SD.

leptic focus, 6 patients underwent sCSM with additional language testing, to prevent inadvertent injury to important fiber pathways. In 5 of the 6 patients, stimulation near the identified AF pathways was possible, but the resected area in the patient in Case 7 was located anterior to the AF; subcortical stimulation of these anterior areas in this patient evoked no deficits. The imaging data from 5 patients in whom subcortical stimulation near the identified AF was delivered (Cases 3, 4, 6, 8, and 9) are shown in Fig. 6.

The subcortical stimulation results may be broken down into 3 categories: 1) subcortical stimulation locations where deficits were evoked and that encompassed a proportion of the identified AF pathways (Fig. 6a–c); 2) subcortical stimulation locations where deficits were evoked but that did not encompass any of the identified AF pathways (Fig. 6d); and 3) subcortical stimulation locations where deficits were not evoked and that did not encompass a sizeable number of the identified AF pathways (Fig. 6e).

Subcortical Stimulation at Sites Including AF Pathways

Case 3. This right-handed woman, who had left-hemisphere language according to fMRI imaging, underwent language mapping followed by resection of a cavernous malformation. After resection, the adjacent white matter, including previously identified AF fiber tracts, was stimulated (Talairach coordinate [−35, −46, +24 mm]). With subcortical stimulation at 10 mA, the patient demonstrated auditory comprehension and encoding deficits. The patient was unable to repeat the sentence “We are all going to see the cinema” and was also unable to produce the correct name after presentation of auditory descriptions: for example, “An animal that goes meow” (cat). Subcortical stimulation was delivered at the same time as the object to be named was described to the patient. There was no deficit in counting numbers, reciting the alphabet, or repeating a phrase if stimulation was delivered only during articulation. This implies a selective deficit in auditory encoding and comprehension. An examination of the fiber pathways passing through the subcortical stimulation site showed that several were part of the identified AF pathways (Fig. 6a).

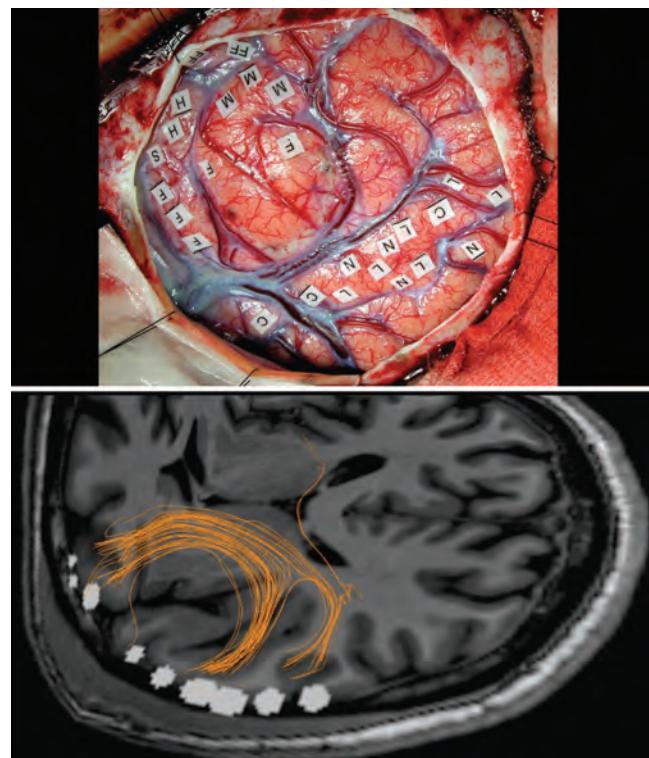


FIG. 4. Intraoperative photograph (*upper*) and MR image (*lower*) showing ELSs with a direct relationship to identified AF pathways. A direct relationship between cortical stimulation sites and the AF tractography pathways is illustrated with an intraoperative photograph of exposed left-hemisphere cortex with labeled sites (*upper*) and an orthogonal view of the patient's T1-weighted MR image (*lower*), with stimulation sites represented as white voxels. Posterior language sites on the superior temporal gyrus are located adjacent to terminations of identified AF pathways, and an anterior speech arrest site is located near the anterior terminations of the AF.

Case 4. This right-handed man, who had left-hemisphere language according to fMRI imaging, underwent CSM of language followed by resection of a glioma. During resection, the adjacent white matter, including previously identified AF fibers, was stimulated at 4 mA (coordinate −38, −7, +34 mm). During stimulation, the patient demonstrated a pronounced loss of articulate speech. This deficit occurred during stimulation while the patient was asked to count out loud and to repeat simple sentences. The fiber pathways passing through the subcortical stimulation site included several that were part of the identified AF pathways (Fig. 6b).

Case 6. This left-handed man, who had left-hemisphere language according to fMRI imaging, underwent right-sided CSM, which revealed no sites where language was disrupted. Following CSM and during resection of a tumor in the parietotemporal region, subcortical stimulation of the adjacent white matter, including previously identified AF fiber tracts, was performed in the right hemisphere. Subcortical stimulation at 3.5 mA (coordinate [+27, −15, +29 mm]) during auditory repetition and picture naming tasks produced no comprehension deficits or speech disruption. Subcortical stimulation evoked a sensory perception of tingling on the patient's left chest

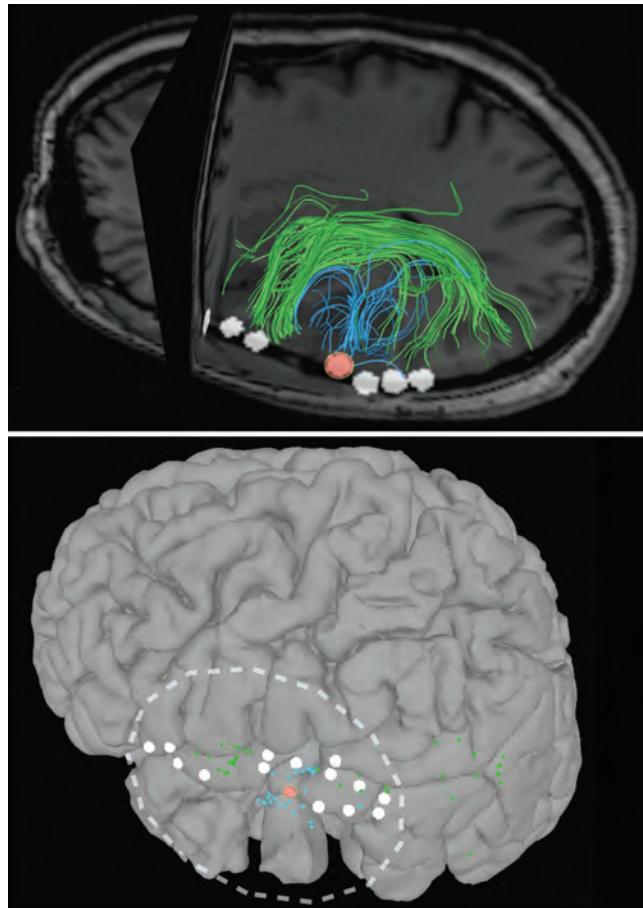


Fig. 5. Case 10. An ELS with an indirect relationship to identified AF pathways. An indirect relationship between pathways in the immediate region of an “L”-labeled cortical stimulation site (red circle) and the AF tractography pathways (green) is shown. *Upper panel* shows an orthogonal view of the T1-weighted MR image, with pathways adjacent to the stimulation site (blue), AF pathways (green), and other essential cortical language sites (white voxels). *Lower panel* shows the terminations of the AF pathways (green) and the terminations of the pathways adjacent to the “L” stimulation site (blue) relative to the cortical surface. *White spheres* on the cortical surface are essential cortical language sites, and the *dashed line* is the approximate boundary of the craniotomy.

and arm, but no language deficit. The fiber pathways passing through the subcortical stimulation site included several that were part of the identified right-sided homolog of the AF (Fig. 6c).

Subcortical Stimulation at Sites Including non-AF Pathways

Case 8. This right-handed woman, who had left-hemisphere language according to fMRI imaging, underwent left hemisphere cortical language mapping followed by resection of a glioma. Following CSM and during resection of a tumor in the frontal lobe, subcortical stimulation of the adjacent white matter close to previously identified AF fiber tracts was performed at 3 locations $[-30, -2, +28 \text{ mm}]$, $[-30, -3, +28 \text{ mm}]$, and $[-31, -3, +27 \text{ mm}]$ at 8.5 mA. At all 3 sites the patient exhibited speech arrest; both repetition and counting were interrupted. The fiber path-

ways passing through the subcortical stimulation sites did not include any of the identified AF pathways, but did include pathways connecting medial frontal cortex (SMA/pre-SMA) to a lateral frontal area adjacent to the anterior part of the identified AF pathways (Fig. 6d).

Case 9. This right-handed man, who had left-hemisphere language according to fMRI imaging, underwent left hemisphere cortical language mapping followed by resection of a glioma. Following cortical stimulation mapping and resection of a tumor in the frontal lobe, subcortical stimulation of the adjacent white matter near previously identified AF fiber tracts was performed at 4 locations $[-36, -2, +22 \text{ mm}]$, $[-30, -2, +29 \text{ mm}]$, $[-32, -1, +35 \text{ mm}]$, and $[-24, -3, +39 \text{ mm}]$ at 9.9 mA. Auditory naming and repetition was tested with stimulation during both the encoding and production phases, and no language deficits were noted at any of these subcortical sites. The fiber pathways passing through the subcortical stimulation sites included corticocortical pathways situated between and lateral to the anterior and posterior terminations of the identified AF (Fig. 6e).

Discussion

In this study, we collected anatomical and DT MR imaging data before surgical intervention and mapped the location of ELSs found during surgery onto the presurgical images to determine the relationship between the ELSs and the AF, a subcortical pathway implicated in language.

The principal novel finding of this study is that the majority of the cortical sites essential for both expressive and receptive aspects of language are closely related to the AF. This finding is significant because it implies that DT imaging-based tractography could be used to predict ELSs based entirely on their close spatial relationship to AF terminations. In such a scenario, cortical terminations of the AF could be identified, along with all pathways that terminated near the AF terminations. A map of candidate eloquent cortical regions could be produced before surgery and then be used to guide intraoperative stimulation. This could potentially increase the accuracy and reduce the time needed to conduct an awake mapping procedure. The generation of such candidate sites from tractography data is feasible using the methods described here, but needs validation in which a much larger data set is used.

Subcortical Stimulation of Subcortical Pathways

A subset of the patients underwent sCSM after cerebral resections to assess language function. Stimulation of identified AF pathways in the dominant hemisphere resulted in expressive and receptive language deficits in 2 patients. In 1 patient, subcortical stimulation in the dominant frontal lobe—proximate to pathways connecting medial and lateral frontal cortices and adjacent to the anterior terminations of the AF—evoked language deficits. Two other patients underwent subcortical stimulation during language testing, but did not show any deficits. This included 1 patient in whom stimulation sites were located far anterior to the most anterior terminations of the AF, and another patient in whom stimulation sites were near a

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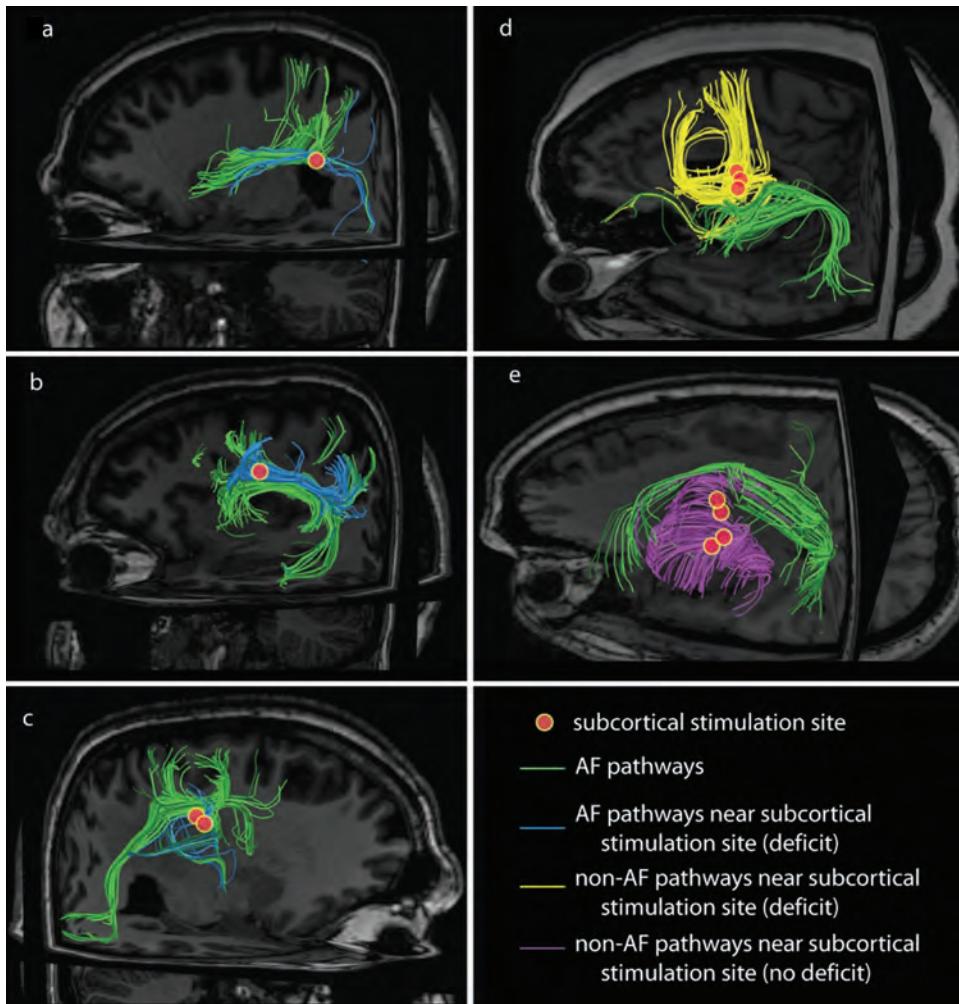


Fig. 6. Images obtained in 5 patients who underwent sCSM, showing the relationship of subcortical stimulation to the AF. The AF pathways are designated by green lines, and approximate locations of sCSM are shown by red circles. In the patients whose imaging studies are shown in panels a–c, subcortical stimulation of AF pathways induced a deficit (patients in a and b had dominant-hemisphere stimulation sites that evoked language dysfunction; the patient in c had nondominant-hemisphere stimulation sites that evoked only sensory percepts). The sCSM in the patient whose imaging study is shown in panel d included mediolateral frontal lobe pathways (yellow) closely related to the anterior terminations of the AF. In the patient whose MR imaging study is shown in panel e, sCSM included a corticocortical set of pathways (purple) nested between the anterior and posterior terminations of the AF.

set of tractography pathways nested between the anterior and posterior terminations of the AF. These subcortical stimulation results show that white matter pathways (in this case the AF) may be localized before surgery by using DT imaging-based tractography, and that functional roles may be explored during resection by targeted stimulation.

Subcortical stimulation allowed us to determine whether a transient disruption of areas near the AF pathways appearing to connect the essential cortical language sites affected language function. However, the small number of patients studied, and the short time that was devoted to subcortical stimulation and language testing, was inadequate to make definitive conclusions about the specific functional role of the AF. Our subcortical stimulation results support the role of the AF as a critical pathway for auditory repetition. However, because of time limitations, in these patients it was not possible to test whether the repetition deficit we

elicited was a function of a disruption in just comprehension, or just production, or both comprehension and production.

Relationship to Other DT Imaging Studies of Language

A few other studies have reported DT imaging-based tractography combined with cortical and subcortical stimulation mapping. In 1 study, tracts from 8 CSM sites in the inferior frontal lobe, stimulation of which produced speech arrest, mouth motor movement, and anomia, were found to terminate in the SMA proper, cerebral peduncle, and the putamen,³⁰ but not in the AF. Two recent studies with large patient sample sizes detailed the use of combined DT imaging¹⁰ with subcortical mapping during surgeries to remove gliomas,⁹ and reported eloquent language areas in a number of stimulated subcortical pathways. However, the focus of these studies was on relating increased accuracy

in subcortical mapping to postoperative outcome, not on how stimulation sites relate to any particular fiber system like the AF.

The AF is not the only subcortical pathway believed to be critical for language function.^{22,38} Both the inferior longitudinal fasciculus and uncinate fasciculus are thought to play important roles in conveying visual information about object identity to frontal speech areas.⁴⁸ In our study, the 21% of ELSs that were found to have no relationship to the AF were located adjacent to tractography pathways, including the inferior longitudinal fasciculus, the uncinate fasciculus, and mediolateral frontal pathways. The existence of language sites with a relationship to these other pathways is consistent with the few studies reporting DT imaging–based tractography combined with intraoperative cortical and subcortical stimulation mapping, and emphasizes that the neural pathways subserving language function do not just include the AF, but represent a much more widespread interconnected system of multiple subcortical pathways. Most cortical stimulation language sites found in our study were located in lateral frontal, temporal, and parietal cortices due to the fact that the craniotomies exposed only these areas for the planned resections. This prevented direct exploration by stimulation mapping of other language regions, such as those in the basal temporal area,^{55,63} a region where other language-related pathways may terminate.

Limitations and Potential Confounding Factors

There exist multiple DT imaging dissection approaches to identifying the AF.^{13,24,37,41} To avoid experimenter bias that is intrinsic to hand-tracing regions of interest in tractography data, we used predefined criteria for constraining the whole-brain connectivity fibers. One limitation of this approach is that it defines the AF as consisting of tractography pathways linking frontotemporal and frontoparietal areas, and ignores a portion of an indirect pathway consisting of 2 components that runs parallel and lateral to the classic AF, and that some regard as also being a constituent of the AF.¹³ The anterior segment of this pathway connects the Broca area with the inferior parietal lobe, and the posterior segment connects the parietal lobe to the Wernicke territory. Our approach includes the anterior segment of the indirect pathway (note tractography pathways from the Broca area to the parietal lobe for 6 of 9 patients who underwent left-hemisphere mapping in Fig. 2a, c, d–f, and h), but does not include pathways of the posterior segment connecting the parietal lobe to the Wernicke area. Inclusion of the posterior segment may have increased the number of cortical stimulation points that were found to be directly located near AF pathways, but given that only 2 of the 9 patients with left-hemisphere language dominance had at least 1 essential language site in the parietal lobe, the increase would probably have been small.

Another limitation of our AF localization method is its reliance on the Broca area as a primary anterior AF termination zone. Neurobiologically driven models of language processing posit that the AF connects other frontal areas, like Brodmann areas 9 and 6, in addition to Brodmann areas 44 and 45.^{31,52} However, the major AF input to the frontal lobe has been documented to arrive

at Brodmann area 44.²⁴ Our choice of the Broca area as a starting point for AF localization was motivated by the public availability of objective cytoarchitectonic templates representing Brodmann areas 44 and 45.²³ As other cytoarchitectonic regions are mapped and their templates made available, it will be possible to expand the array of termination zones that have been implicated in language function.

The use of DT imaging in patients with tumors may be problematic because tumors may not only cause deviations in the normal course of tracts but may also change the diffusivity signal that is used to reconstruct the tractography streamlines.⁵⁹ However, depending on the tumor type, the adjacent white matter may be structurally preserved,⁴³ and at least 1 case report has shown that DT imaging may be used to discern glioblastoma multiforme tumor tissue from adjacent white matter of the superior longitudinal fasciculus, of which the AF is a subcomponent, and preserve language function following resection.¹⁸

Finally, our study includes results from 9 patients who were found to have ELSs in the left hemisphere. This is a small but growing number of patients, and caution should be taken in the interpretation and in the preliminary nature of the findings.

Conclusions

A close correspondence was found between the majority of essential cortical language sites and the terminations of the AF as measured by DT imaging–based tractography. Additionally, stimulation of subcortical white matter in the dominant hemisphere, including and adjoining the AF, resulted in expressive and receptive deficits, implicating the AF in language function. The finding that AF pathway termination locations correlate with areas that are essential to language fluency is significant because it means that ELSs may be predicted before surgery by using DT imaging, thereby improving the efficiency and accuracy of awake mapping procedures.

Disclosure

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