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Evaluating syntactic comprehension during awake intraoperative cortical stimulation mapping

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Abstract

OBJECTIVE—Electrocortical stimulation mapping (ECS) is widely used to identify essential language areas, but sentence-level processing has rarely been investigated.

METHODS—While undergoing awake surgery in the dominant left hemisphere, 6 subjects were asked to comprehend sentences varying in their demands on syntactic processing.

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Author Contributions

Conception and design: Riva, Chang. Acquisition of data: Riva, Cai, Castellano, Jordan, Berger, Chang. Analysis and interpretation of data: Riva, Wilson, Castellano, Chang. Drafting the article: Riva, Wilson, Cai. Critically revising the article: Riva, Wilson, Henry, Gorno Tempini, Berger, Chang. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Riva. Statistical analysis: Wilson. Study supervision: Chang.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

RESULTS—In all 6 subjects, stimulation of the inferior frontal gyrus disrupted comprehension of passive sentences, which critically depend on syntactic processing to correctly assign grammatical roles, without disrupting comprehension of simpler tasks. In 4 of the 6 subjects, these sites were localized to the pars opercularis. Sentence comprehension was also disrupted by stimulation of other perisylvian sites, but in a more variable manner.

CONCLUSIONS—These findings suggest that there may be language regions that differentially contribute to sentence processing and which therefore are best identified using sentence-level tasks. The functional consequences of resecting these sites remain to be investigated.

Keywords

syntax; sentence; cortical stimulation mapping; awake brain surgery; language; surgical technique

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Electrocortical stimulation mapping (ECS) is widely used during resective surgery to identify essential language areas.[1-6] The most commonly used tasks are counting and picture naming, which are automatic speech- and word-level tasks, respectively. Although real-life language use involves combining words into phrases and sentences, language processes beyond the word level have been assessed only rarely when carrying out ECS.[7,8]

Stimulation of the posterior inferior frontal gyrus (IFG) was recently found to result in syntactic errors in sentence production, even in sites where stimulation did not interfere with word-level language processes.[9] An earlier study also demonstrated that stimulation of the posterior IFG could interfere with sentence comprehension.[10,11] In contrast, investigators who have used ECS with sentence comprehension tasks[12] or naming with auditory description tasks, both of which entail sentence comprehension,[13-15] have reported that these tasks were disrupted by stimulation of posterior temporal and inferior parietal sites.

The goal of this preliminary study was to identify brain regions where ECS interferes with sentence comprehension. In 6 subjects who were undergoing awake craniotomy with language mapping for resection of brain tumors or epileptogenic foci, we presented sentences for comprehension while stimulating frontal, temporal, and parietal regions. Unlike previous studies, we presented matched sentences under three different conditions that systematically varied the extent to which a correct response depended on an intact ability to process syntactic information. We also investigated the anatomical connectivity of the sites identified, using diffusion tensor imaging.

Methods

Participants

Six subjects (4 male, 2 female; mean age 37.2 ± 14.2 years) underwent awake craniotomy with language mapping for resection of brain tumors or epileptogenic foci at the University of California, San Francisco (UCSF). All subjects had left hemisphere surgical sites, temporal in 4 subjects and frontal in 2 subjects. Five subjects presented with seizures and 1 subject with a focal neurological deficit. Four subjects had gliomas and 2 subjects had medically refractory epilepsy. All subjects provided written informed consent. The study was approved by the UCSF Institutional Review Board. The research was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the institution.

All subjects were adult native speakers of English. Each subject underwent a preoperative speech and language test battery along with a neuropsychological assessment, and all performed in the normal range. All subjects had left hemisphere language dominance, as assessed through magnetoencephalography.[16] No subjects had presenting or preoperative symptoms of aphasia, as evaluated with the Western Aphasia Battery.

Intraoperative Stimulation Mapping

A monitored anesthesia care regimen was used. Stimulation mapping was performed after checking subject responsiveness. The intraoperative syntactic task was administered following motor and language mapping (counting, object naming, single-word repetition). Counting, picture naming, and repetition were also performed to determine the specificity of any disturbances of syntactic comprehension.

Intraoperative stimulation mapping was performed on the exposed cortex with an Ojemann stimulator (Integra LifeSciences, 60 Hz, bipolar probe, biphasic pulses). The stimulation threshold was determined for each patient, typically between 2 and 5 mA, and set at a level eliciting speech arrest without causing afterdischarges, which were monitored with intraoperative electrocorticography. Speech arrest was defined as the involuntary cessation of speech output during counting, without observed movement of the vocal tract articulators.[2] Two high-definition video cameras recorded the mapping procedures, one focusing on the cortical surface in the surgical field and the other on the subject’s face.

Intraoperative Syntactic Task

Syntactic comprehension was assessed intraoperatively using a two-alternative forced-choice auditory sentence-to-picture matching task[17] tailored for the intraoperative setting. Each trial began with the presentation of two pictures: a target and a foil. The pictures were marked A and B. One second after the picture presentation, an audio recording of a sentence matching one of the two pictures was played through a set of speakers. Subjects were then asked to say “A” or “B” to indicate which picture matched the sentence they had heard (Fig. 1).

We evaluated three conditions that differed in their syntactic complexity (Fig. 2), labeled as lexical, active, and passive. All conditions were matched for length, lexical content, and the point at which the sentence disambiguated between the target and foil pictures. All sentences were constructed using just 2 high-frequency nouns (boy, girl) and 1 of 7 high-frequency verbs (push, pull, kiss, kick, chase, wash, hug) to keep lexical demands to a minimum.

Before surgery, all 6 subjects completed baseline trials of the syntactic task without any errors. For the intraoperative task, the stimuli conditions were presented in triplets. Each triplet contained a lexical, an active, and a passive item. The three conditions were presented in a random order within each triplet. ECS was applied at the onset of the auditory sentence and lasted for the duration of the sentence.

ECS was applied broadly over the exposed cortex in the craniotomy. The craniotomy exposed frontal, temporal, and parietal areas to different extents according to clinical needs and surgical indications. The locations of the ECS sites where stimulation interfered with language function were marked with a sterile paper label. The locations were recorded with 3D DICOM coordinates registered in the stereotactic neuronavigation system (Brainlab AG), along with an intraoperative picture.

Intraoperative Stimulation Mapping Data Analysis

Intraoperative trials with incorrect responses or no responses were treated equivalently, and sites where stimulation induced either incorrect responses or no responses were considered eloquent. We examined accuracy as a function of stimulation site and condition. Inferior frontal language regions were defined as the pars opercularis and pars triangularis of the IFG. Temporal language regions were defined as the middle and posterior superior temporal gyrus (STG) and the middle temporal gyrus (MTG). Other sites that were stimulated were the ventral premotor area, the middle frontal gyrus, the anterior STG, and the inferior parietal lobule.

Neuroradiological Protocol and Image Processing

MRI was performed preoperatively and postoperatively on a Signa 3T scanner (General Electric). MRI acquisition and processing were performed as previously described.[18,19] High angular resolution diffusion imaging (HARDI) data sets were processed and analyzed with Diffusion Imaging in Python (Dipy), q-ball residual-bootstrap fiber tracking,[20] and FSL linear and nonlinear transformations (FMRIB's FLIRT and FNIRT registration tools).[21] Tracking was regulated using a fractional anisotropy threshold of 0.15 and a maximum angle of 60° as stopping parameters in the algorithm.[19] The results were visualized with Trackvis (http://trackvis.org).

Each site for which the results were eloquent for passive sentences was used for fiber tracking along with conventional anatomical landmarks. The 3D DICOM coordinates of the cortical sites that were eloquent for passive sentences during ECS were stored intraoperatively and then transferred to the HARDI sequence. Postoperatively, a region of interest (ROI; average size 15 × 15 mm) was created offline by dilating the eloquent cortical site of 4 mm to include underlying white matter and to intercept the cortico-subcortical termination points of a given streamline. The ROI was used as an additional seed region to constrain probabilistic fiber tractography; after having run the conventional workflow, tractography was repeated, keeping only the streamline contacting both the anatomical landmarks and the additional seed point obtained with ECS.

Results

Case Series

Intraoperative photographs of the exposed cortical surfaces of the 6 subjects are shown in Fig. 3. The following brief descriptions highlight regions where consistent and specific effects of stimulation on syntactic comprehension were observed.

In subject 1, stimulation of a site in the pars opercularis of the IFG disrupted comprehension of two passive trials and one active trial but did not disrupt counting or single-word tasks. Another site in the mid-STG disrupted comprehension of two passive trials but was not tested for other functions.

In subject 2, stimulation of a site in the dorsal pars opercularis disrupted comprehension of seven passive trials but did not disrupt three active trials, one lexical trial, or counting or single-word tasks. Stimulation of a more ventral site in the pars opercularis disrupted three active trials but did not disrupt three passive trials. Stimulation throughout the STG disrupted four active trials, but other conditions were not tested.

In subject 3, stimulation of the ventral premotor cortex disrupted three passive trials but did not disrupt three active trials, two lexical trials, or counting or single-word tasks.

In subject 4, stimulation of a site in the pars opercularis disrupted six passive trials but did not disrupt two active trials, one lexical trial, or counting or single-word tasks. Passive trials were also disrupted more often than not when a range of temporal, parietal, and more anterior frontal regions were stimulated.

In subject 5, stimulation of a site in the middle frontal gyrus disrupted two passive trials but did not disrupt two active trials, one lexical trial, or counting or single-word tasks.

In subject 6, stimulation of the pars opercularis and pars triangularis of the IFG disrupted comprehension in six passive trials but did not disrupt comprehension in four active trials, two lexical trials, or counting or single-word tasks.

Summary Across Subjects

A total of 371 syntactic comprehension trials were administered across the 6 subjects. Among these, 252 trials were performed with ECS applied over frontal, temporal, or parietal regions, and 119 trials were performed without stimulation and served as an intraoperative baseline. The effect of stimulation as a function of condition and brain region is shown in Fig. 4.

In the lexical condition, where decisions could be made based on semantic information of lexical items alone, no errors were made in the absence of stimulation (40 trials), and only 4 errors were made on the 71 trials with stimulation (6%). The effect of stimulation was not statistically significant for this condition ($p = 0.29$, Fisher exact test).

In the active condition, which involved some syntactic contribution to comprehension, there were 2 errors on 39 trials (5%) in the absence of stimulation and 19 errors on 82 trials (23%) in the presence of stimulation. The effect of stimulation was statistically significant for this condition ($p = 0.019$, Fisher exact test). Errors were most prevalent after stimulation of temporal language sites (10 errors on 22 trials, 45%), followed by frontal language sites (6 errors on 28 trials, 21%) and then other sites (3 errors on 32 trials, 9%). The difference in error rates between the sites was statistically significant (chi-square 9.61, $p = 0.0082$).

In the passive condition, in which comprehension depended on noncanonical syntactic structures, there were 5 errors in 39 trials (13%) in the absence of stimulation and 43 errors in 100 trials (43%) in the presence of stimulation. The effect of stimulation was statistically significant for this condition (p = 0.0007, Fisher exact test). Errors were most prevalent after stimulation of frontal language sites (27 errors in 48 trials, 56%), followed by temporal language sites (8 errors in 17 trials, 47%) and then other sites (8 errors in 35 trials, 23%). The difference in error rates between the sites was statistically significant (chi-square 9.35, p = 0.0093).

Probabilistic Tractography and Electrocortical Stimulation

HARDI q-ball probabilistic fiber tractography was performed postoperatively. In all subjects, throughout all eloquent sites obtained with ECS, fibers belonging to the dorsal fasciculi were obtained (Fig. 5). Fibers belonging to the arcuate fasciculus were found in all subjects; however, particularly when seed ROIs were present in the opercular part of Broca's area, streamline of the superior longitudinal fasciculus (SLF) was also tracked.

Discussion

Our main finding was that in all 6 subjects, we observed left frontal sites where cortical stimulation disrupted comprehension of passive sentences but did not disrupt comprehension of simpler sentences, counting, or single-word tasks. Because passive sentences deviate from the canonical word order in English, correctly assigning arguments to grammatical roles depends critically on syntactic processing. In 4 subjects, these sites were found in the pars opercularis, whereas in the remaining 2 subjects, similar sites were observed in the adjacent ventral premotor cortex or middle frontal gyrus.

One possible interpretation of these data would be that there are regions of the left inferior frontal cortex that are specialized for syntactic processing. A recent ECS study demonstrated that syntactic errors were elicited by stimulation of the pars opercularis.[9] The results of the present study could be taken to suggest that the role of IFG in syntax spans both production and comprehension of syntactic structures.[22] Indeed, numerous functional imaging[23] and lesion-symptom mapping studies[24] have been argued to support this view.

However, more recent and larger-scale lesion studies suggest that syntactic comprehension deficits follow more reliably from posterior temporoparietal damage than frontal damage.[25-27] An alternative hypothesis is that parts of the IFG have a "language executive" role.[28] According to this view, the IFG might be involved in regulating many aspects of linguistic processing, such that stimulation of the IFG causes dysregulation throughout the language network. The emergence of deficits at the sentence level might reflect the greater degree of coordination that is required as larger linguistic units are assembled. The language executive role of the IFG, while readily observed in normal language function, does not appear to be essential, since neither grammatical deficits nor severe language deficits of any kind follow from damage that is relatively circumscribed in this region.[29]

The consequences of resecting brain regions where stimulation interrupts syntactic processes but not word-level processes or speech are not known. Language outcomes are generally good after substantial resections in the IFG in subjects in whom language was mapped with speech- and word-level tasks,[30,31] but not sentence tasks.[30] However, it would be worthwhile for future studies to examine whether expanding intraoperative mapping protocols to include sentence-level tasks can lead to improved outcomes.

Diffusion tensor imaging showed that the frontal sites where stimulation disrupted syntactic comprehension projected primarily to dorsal tracts connecting frontal and temporal regions, in particular the arcuate fasciculus and SLF. This finding is consistent with the finding of a previous study reporting that degeneration of these tracts is associated with syntactic deficits,[32] bearing in mind the many other roles these tracts play in language and cognition.[33]

Our study is preliminary in nature and has several important limitations. First, we studied only 6 subjects, which limited our ability to draw conclusions about the population. Second, the range of brain regions explored differed across subjects and was determined by clinical needs and surgical indications. Although left frontal regions were probed in all subjects, the extent to which other perisylvian regions were stimulated was variable across subjects and sparse in most of our cases. Third, although we provided some evidence for specificity of the syntactic sites we observed, we performed relatively few stimulations at each site. Finally, direct subcortical stimulation should be further deployed to properly address whether a selective contribution to syntactic processing between the arcuate fasciculus and the SLF exists. Despite these limitations, our study provides initial evidence that there are brain regions where cortical stimulation can disrupt the comprehension of more syntactically complex sentences, without interfering with simpler sentences, word-level processes, or speech.

Conclusions

This brain mapping study showed that sentence-level tasks could better identify the differential contribution of cortical frontotemporal areas to sentence processing than word-level tasks.

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ABBREVIATIONS

ECS	electrocortical stimulation mapping
HARDI	high angular resolution diffusion imaging
IFG	inferior frontal gyrus
MTG	middle temporal gyrus
ROI	region of interest

SLF	superior longitudinal fasciculus
STG	superior temporal gyrus
UCSF	University of California, San Francisco

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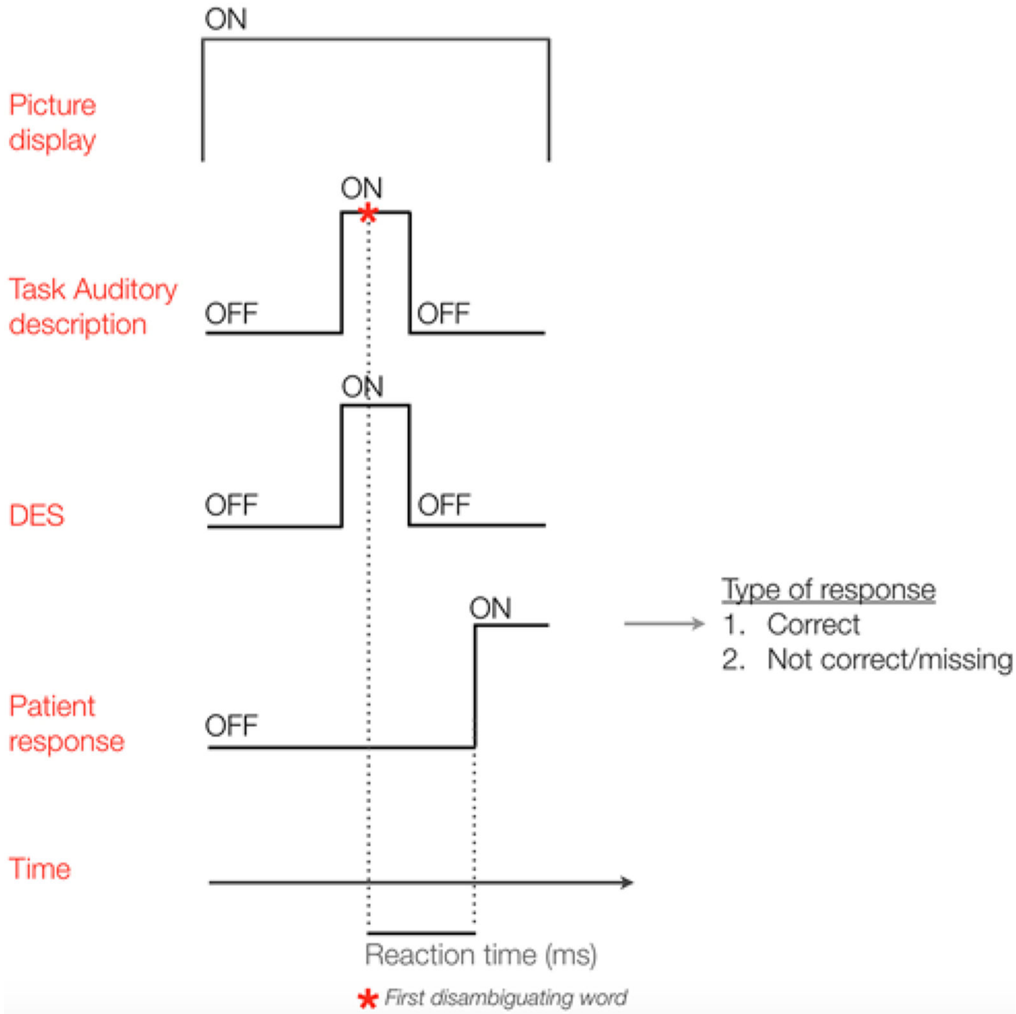

FIG. 1.
Structure of each trial.

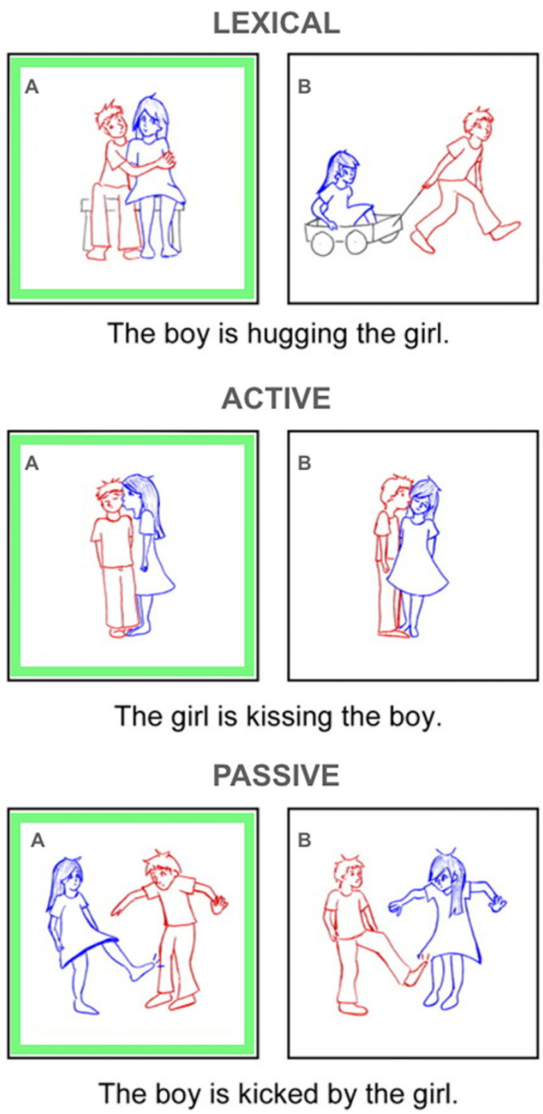

FIG. 2.

Experimental design. There were three conditions (labeled as lexical, active, or passive) that differed in their syntactic complexity. The first condition was labeled *lexical* because it involved canonical sentences in which the correct response could be determined based on lexical information (e.g., “The boy is hugging the girl,” with the foil picture showing a different action, e.g., pulling). In the second condition, labeled *active*, the foil pictures contained the same lexical items as the target pictures; it was necessary for the listener to attend to syntactic structures to reach the correct response. Nevertheless, the syntactic structures involved were canonical: elements were arranged in configurations that are prototypical in English (e.g., “The boy is hugging the girl,” with the foil picture showing the same action but with different syntax, with the agent and patient reversed). The third condition, labeled *passive*, also required processing of syntactic structures to determine the correct response, but now the structures involved were noncanonical: elements were displaced from their prototypical positions, since the patient was initial and agent was in a prepositional phrase, thus requiring attention to passive morphosyntax (e.g., “The boy is hugged by the girl," with the foil picture showing the same action but with the agent and patient reversed). The targets are shown on the left, surrounded by a *green box*. In the actual experiment, targets and foils were presented randomly on the left or right; an audio recording of a sentence matching one of the two pictures was played. Subjects were then asked to say "A" or "B" to indicate which picture matched the sentence they had heard.

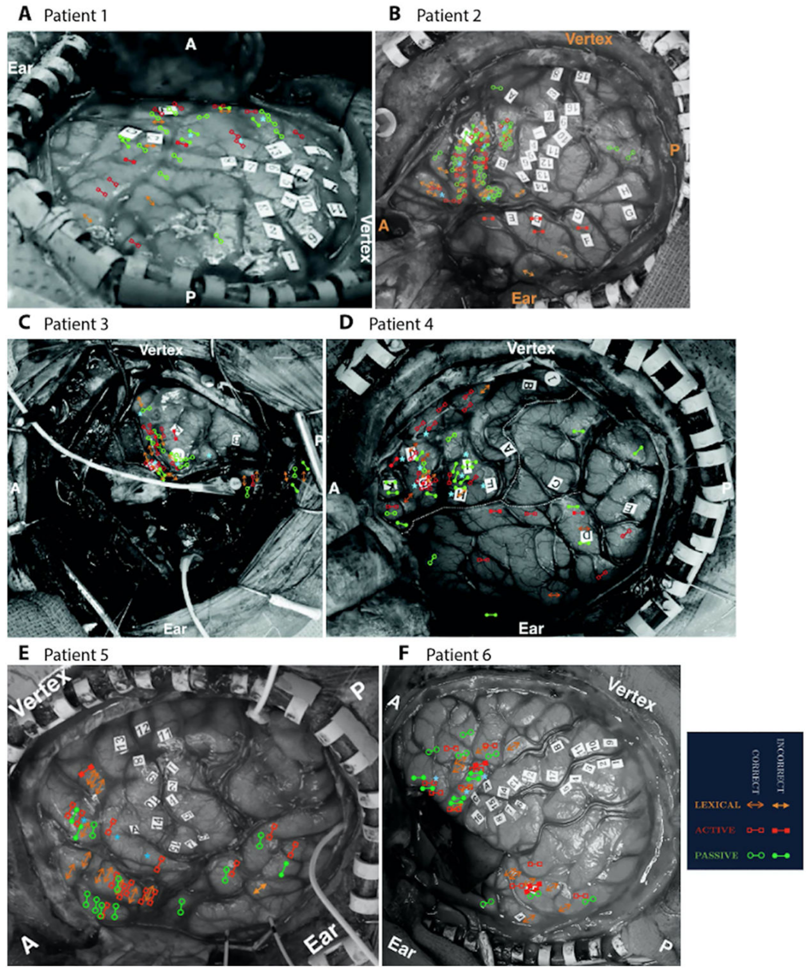

FIG. 3.

Stimulation sites and outcomes for each of the 6 subjects. Each intraoperative photograph was taken during the craniotomy. Motor, sensory, and language sites are marked. Lexical, active, and passive sentence comprehension trials are shown in *orange*, *red*, and *green*, respectively, with *filled symbols* indicating error trials and *unfilled symbols* indicating correct trials. *Blue asterisks* denote sites where speech and single-word language tasks were preserved on stimulation.

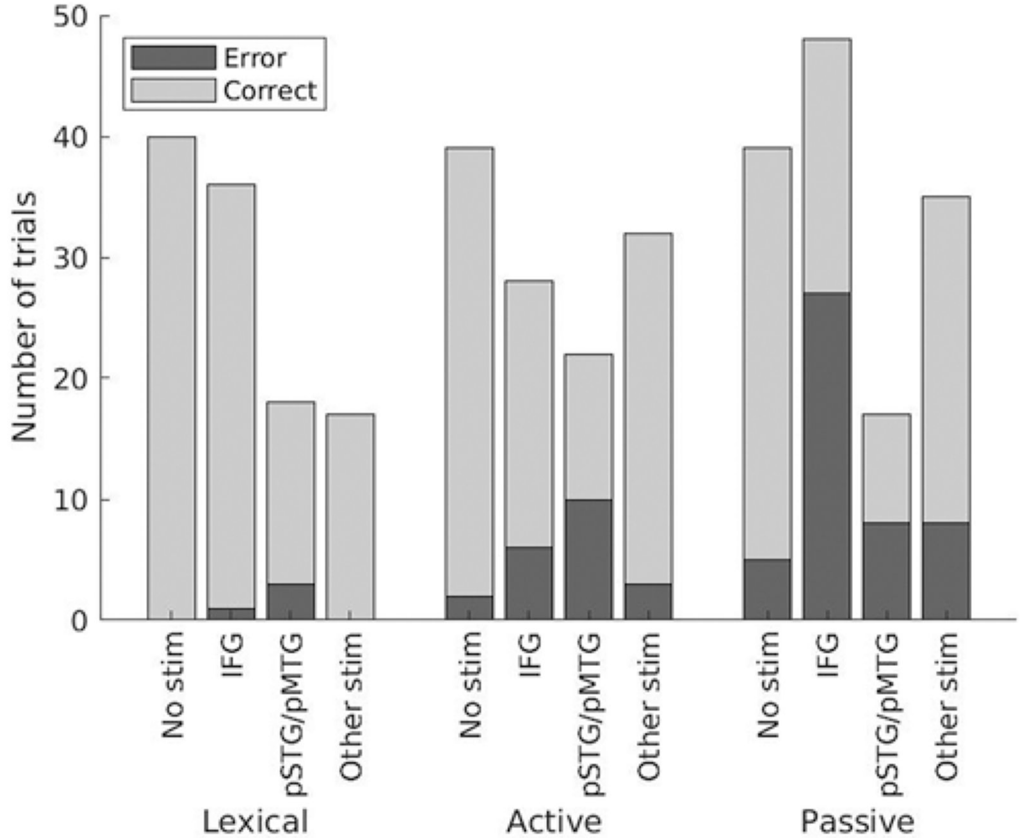

FIG. 4.

Summary of errors and correct responses by condition and stimulation (stim) site. pMTG = posterior middle temporal gyrus; pSTG = posterior superior temporal gyrus.

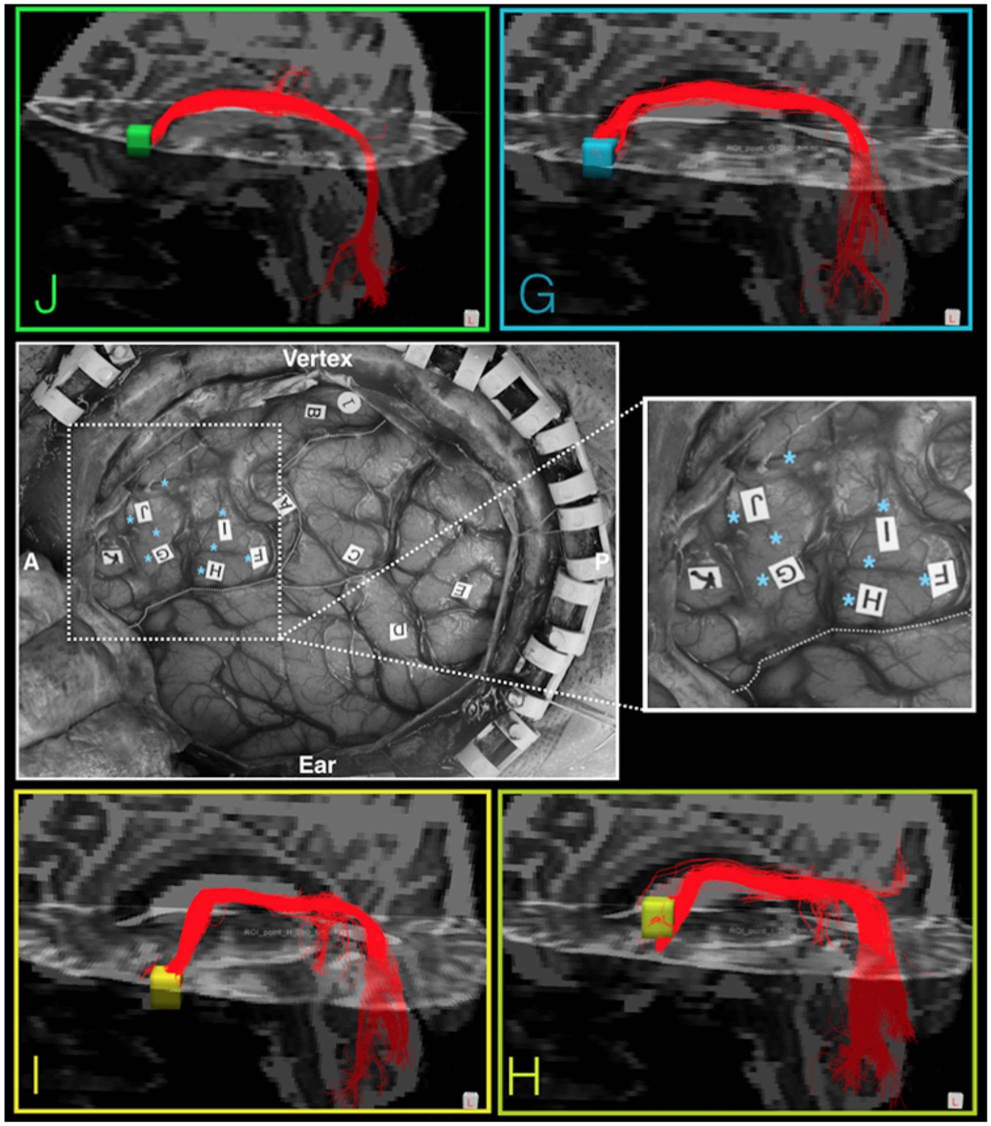

FIG. 5.
Probabilistic tractography and electrocortical stimulation. The surgical field of subject 4 is depicted with alphanumerical tags marking the point of ECS-elicited responses for the neurological functions tested. An **enlarged view** is also provided. *Asterisks* mark sites where ECS did not determine counting or naming arrest during stimulation. Four sites consistently disrupted the performance of the test during the comprehension of passive sentences. In two of those (**G and J**), *highlighted fibers* belong to the arcuate fasciculus when used for postoperative tractography; in the others (**H and I**), *highlighted fibers* are intercepted fibers of the SLF.