Spatial-temporal functional mapping of language at the bedside with electrocorticography

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ABSTRACT

Objective: To investigate the feasibility and clinical utility of using passive electrocorticography (ECoG) for online spatial-temporal functional mapping (STFM) of language cortex in patients being monitored for epilepsy surgery.

Methods: We developed and tested an online system that exploits ECoG's temporal resolution to display the evolution of statistically significant high gamma (70–110 Hz) responses across all recording sites activated by a discrete cognitive task. We illustrate how this spatial-temporal evolution can be used to study the function of individual recording sites engaged during different language tasks, and how this approach can be particularly useful for mapping eloquent cortex.

Results: Using electrocortical stimulation mapping (ESM) as the clinical gold standard for localizing language cortex, the average sensitivity and specificity of online STFM across 7 patients were 69.9% and 83.5%, respectively. Moreover, relative to regions of interest where discrete cortical lesions have most reliably caused language impairments in the literature, the sensitivity of STFM was significantly greater than that of ESM, while its specificity was also greater than that of ESM, though not significantly so.

Conclusions: This study supports the feasibility and clinical utility of online STFM for mapping human language function, particularly under clinical circumstances in which time is limited and comprehensive ESM is impractical. *Neurology*® 2016;86:1181–1189

GLOSSARY

ECoG = electrocorticography; **ESM** = electrocortical stimulation mapping; **HG** = high-gamma; **ROI** = region of interest; **STFM** = spatial-temporal functional mapping.

Functional human brain mapping is commonly performed during or prior to invasive brain surgery for the treatment of drug-refractory epilepsy^{1,2} and brain tumors.³ The current gold standard, electrocortical stimulation mapping (ESM), is time-consuming^{4,5} and often induces afterdischarges or seizures.^{4,6,7} Additionally, it is difficult to rule out distant effects through diaschisis or action potentials evoked by stimulation.^{7–9} These limitations have long motivated the investigation of passive electrocorticographic (ECoG) recordings as a tool for rapidly and safely mapping cortical function prior to resective surgery.^{10–12}

Here we introduce and test the feasibility and clinical utility of an online trial-based system for spatial-temporal functional mapping (STFM) of language cortex. High-gamma (HG, ~60–200 Hz) power changes have been demonstrated to be a robust and reliable index of task-related activation of cortical populations of neurons with high spatial and temporal specificity.^{13,14} The STFM system builds upon previous passive ECoG mapping software^{15–18} by providing a trial-based framework for online display and statistical validation of HG dynamics.

In 7 patients, estimates of the system's sensitivity and specificity for language mapping, relative to the benchmark of ESM, were the same or better than previous reports.^{18–21} Moreover, we found that relative to predefined language cortex boundaries, the sensitivity and specificity of

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Supplemental data
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STFM were greater than that of ESM, though the increase in specificity was not statistically significant.

METHODS Patients and clinical settings. Seven English-speaking patients (table e-1 on the *Neurology*[®] Web site at Neurology.org) with intractable epilepsy underwent placement of subdural electrodes in the dominant hemisphere to localize their ictal onset zone and to identify language and motor areas using ESM. The implanted electrodes consisted of arrays of macroelectrodes (2.3 mm exposed diameter, 1 cm spacing, Adtech [Racine, WI] or PMT Corp. [Chanhassen, MN]). In 5 of 7 patients, the macroelectrodes were supplemented by 4 × 4 arrays of microelectrodes (75 μm diameter, 0.9 mm spacing, PMT Corp.). In all patients, the anatomical placement of electrodes was dictated solely by clinical considerations for recording seizures or mapping cortical function.

Standard protocol approvals, registrations, and patient consents. Patients were admitted to the Johns Hopkins Epilepsy Monitoring Unit after electrode implantation for a period of 6–14 days. All patients gave informed consent to participate in research testing under a protocol approved by the institutional review board of the Johns Hopkins Medical Institutions.

Experimental testing and event markers. In this study, the online STFM system performed functional mapping during 2 distinct behavioral tasks. During visual object naming, patients were shown a picture on a monitor directly in front of them during each trial, and were instructed to speak the name of the object in the picture. The stimulus onset was determined by a thresholded output from a photodiode mounted on the monitor presenting the stimuli. During auditory word repetition, patients were played an audio recording of a spoken word through insert earphones designed to attenuate external background noise during each trial, and were instructed to verbally repeat the cued word. The stimulus onset was determined by trigger pulses synchronized with the onset of the auditory stimuli in a separate channel. Intertrial intervals (time from the start of a trial to the start of the next trial) ranged 6.5–8.2 seconds for visual object naming and 7.9–8.0 seconds for auditory word repetition. Patients completed a range of 55–251 trials for visual object naming and 96–116 trials for auditory word repetition, as governed by time constraints on patient testing and the set of stimuli used. Trials affected by artifacts or interruptions could be removed using the remove trial button on the system graphical user interface.

Electrode localization. Electrode locations were identified in a high-resolution postoperative brain CT, and then transformed onto a high-resolution preoperative brain MRI by volumetrically coregistering the preoperative and postoperative scans in Bioimage Suite.²² One or more viewpoint snapshots were then aggregated into a single image to visualize functional activations relative to individual anatomy.

Visualization. Data acquisition and analysis, spectral feature extraction, and statistical analysis of the online STFM system are described in detail in the e-Methods (figures e-1 and e-2). Raster plots (figure 1) display the magnitude of event-related changes in the HG amplitude at each time point after stimulus onset, as compared to the baseline. These rasters display either trial-averaged amplitude changes (figure 1, rows represent electrodes) or single-trial amplitude changes (figure 3, rows represent trials). The magnitudes are thresholded for significance ($p < 0.05$) using false discovery rate correction in the channel raster and are

uncorrected in the trial raster. Video 1 shows the evolution of the statistically significant HG responses obtained as the number of trials grew during visual object naming in patient 1.

To facilitate clinical interpretation of time-varying cortical activity displayed by STFM, a brain map was displayed alongside the channel raster to show the locations and relative magnitudes of activations either integrated over the entire poststimulus interval or at any user-selectable time point in the channel raster. In figures 1 and 2, early and late task stages have been modified offline, with the early stage beginning at stimulus onset and the late stage beginning at the mean speech onset and ending at the mean speech offset. The end of the early stage was chosen to maximize exclusion of sites that were prominently activated during the late stage. The magnitude of the HG response at a particular electrode and time is represented by the size and color of disks overlaid on ECoG electrode locations in a 2D snapshot of the 3D brain reconstruction.

ECoG maps vs electrical stimulation maps. To investigate the degree of correspondence between STFM and ESM, the sensitivity and specificity of STFM were computed using ESM as the gold standard. In this analysis, sensitivity was calculated as the proportion of ESM+ sites correctly identified as STFM+; specificity was the proportion of ESM− sites correctly identified as STFM−:

$$\text{Sensitivity} = \frac{\text{STFM}^+/\text{ESM}^+}{\text{STFM}^+/\text{ESM}^+ + \text{STFM}^-/\text{ESM}^+} \quad (1.1)$$

$$\text{Specificity} = \frac{\text{STFM}^-/\text{ESM}^-}{\text{STFM}^+/\text{ESM}^- + \text{STFM}^-/\text{ESM}^-} \quad (1.2)$$

A site was marked STFM+ if it exhibited a significant task-related HG amplitude increase. A site was marked ESM+ if stimulation at this site inhibited language or inhibited or elicited movements or sensations in face, tongue, or mouth. At sites categorized as ESM+ by bipolar stimulation (stimulation between 2 adjacent electrodes), either electrode being STFM+ resulted in both electrodes being labeled as STFM+/ESM+. Only one of these electrodes was counted towards the sensitivity since stimulation could have interfered with neural processing at either or both sites. In contrast, when pairs of electrodes were ESM− during bipolar stimulation, each electrode was marked independently as either STFM+ or STFM−. STFM of visual object naming was compared with ESM of picture naming. STFM of auditory word repetition was compared with ESM of comprehension and spontaneous speech, since auditory word repetition was not part of the standard battery of language tests used for ESM.

Region of interest (ROI) analysis. For each patient, we performed an anatomical ROI analysis to compare both ESM and STFM results to regions where cortical lesions most consistently impair language function in the literature. Task-relevant ROIs for auditory word repetition included the Broca area, sensorimotor cortex, and Wernicke area, whereas the task-relevant ROIs for visual object naming included those from auditory word repetition in addition to the middle third of basal temporal-occipital cortex (yellow shaded areas in figures 1 and 2). The middle third was adopted as a convenient and inclusive boundary for inclusion of higher-order visual cortex responsible for visual object processing.^{23,24} For this analysis, the Wernicke area was defined here as the posterior half of the superior temporal gyrus, supramarginal gyrus, and angular gyrus (blue shaded areas). The Broca area included pars triangularis and pars opercularis of the left inferior frontal gyrus (green shaded areas). Relevant sensorimotor cortex (red shaded areas) included precentral and

Figure 1 Spatial-temporal functional mapping (STFM) in patient 1

STFM of visual object naming (A) and auditory word repetition (B) in patient 1. STFM results are shown as a raster of high-gamma (HG) responses on the left and as brain maps of HG response magnitude (represented by disc size and color) on the right. Electrocortical stimulation mapping (ESM) maps (colored bars between electrodes) are also shown. Color-shaded areas denote anatomical boundaries of classical language areas used as regions of interest (ROI) in ROI sensitivity/

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postcentral gyri inferior to hand knob of central sulcus (red highlighted sulci).

Each stimulation site (i.e., monopolar or bipolar) was classified as ESM+ or ESM−, and was considered either ROI+ when at least one of the stimulating electrodes was inside the ROIs, or ROI− otherwise. Each monopolar stimulation site was considered STFM+ when the site exhibited a significant task-related HG amplitude increase; bipolar stimulation sites were counted only once and were considered STFM+ when at least 1 of the 2 electrodes was activated.

Using the classification of inside or outside language ROIs as a rough diagnostic standard, we calculated the sensitivities and specificities of STFM and ESM for all stimulation sites across all patients. Sensitivity was calculated as the proportion of stimulation sites in task-relevant ROIs correctly classified as positive; specificity was calculated as the proportion of stimulation sites outside task-relevant ROIs correctly classified as negative:

$$\text{Sensitivity (STFM)} = \frac{\text{STFM}^+/\text{ROI}^+}{\text{STFM}^+/\text{ROI}^+ + \text{STFM}^-/\text{ROI}^+} \quad (2.1)$$

$$\text{Sensitivity (ESM)} = \frac{\text{ESM}^+/\text{ROI}^+}{\text{ESM}^+/\text{ROI}^+ + \text{ESM}^-/\text{ROI}^+} \quad (2.2)$$

$$\text{Specificity (STFM)} = \frac{\text{STFM}^-/\text{ROI}^-}{\text{STFM}^+/\text{ROI}^- + \text{STFM}^-/\text{ROI}^-} \quad (2.3)$$

$$\text{Specificity (ESM)} = \frac{\text{ESM}^-/\text{ROI}^-}{\text{ESM}^+/\text{ROI}^- + \text{ESM}^-/\text{ROI}^-} \quad (2.4)$$

The McNemar χ^2 test²⁵ was performed to assess the statistical discordance of the sensitivities and specificities of STFM and ESM relative to language ROIs.

RESULTS STFM can be performed online. In all patients, our STFM system successfully produced spatial-temporal functional maps of language function that could be reviewed online. Trial-based signal analyses, statistical testing, and STFM visualization were updated between trials. Figure e-3 shows an unmodified screenshot of the online STFM system. Modified screenshots of online STFM during both tasks in patient 1 are shown in figure 1. In each illustration, a screenshot of the channel raster of ECoG activation has been modified to (1) highlight temporally clustered responses evident during online

STFM and (2) compare online STFM to the results from ESM. ROIs are also highlighted as described in Methods. Simplified brain maps for patients 2–7 are shown in figure 2, with online STFM and ESM results from visual object naming and auditory word repetition, respectively. Video 2 shows the frame-by-frame temporal evolution of cortical activation–associated visual object naming in patient 1.

Spatial-temporal functional maps are task-specific. In all patients, online STFM revealed the temporal evolution of activation across all ECoG recording sites. As expected, the different components of each patient's cortical language networks were activated with different temporal envelopes, resulting in complex, cascading spatial-temporal patterns of activation. When functional maps for different language tasks were compared, their differences reflected the contrasting processing demands of the tasks. The STFM system highlighted cortical regions associated with visual processing (basal temporal-occipital cortex) during object visual naming (figures 1A and 2A), speech processing (Wernicke area) during auditory word repetition (figures 1B and 2B), and speech planning and preparation (Broca areas and sensorimotor cortex) during both tasks (figures 1B and 2B).

Micro-ECoG vs macro-ECoG responses: Similarities and differences. The overall response patterns within micro-ECoG arrays were consistent with those of macroelectrodes, and both were consistent with task-related processing demands. However, HG responses within micro-ECoG arrays were often more robust than those within macroelectrodes. This was most evident in single-trial responses, in which statistically significant responses occurred more consistently across time windows and across trials (figure 3). This could have been due to greater temporal and functional homogeneity in population responses within micro-ECoG arrays than those within macroelectrodes. Micro-ECoG arrays sampled cortical activity from a surface area (2.7 mm²) only slightly larger than that of individual macroelectrodes

Figure 1 legend, continued:

specificity analysis. Each raster plot displays the spatial-temporal distribution of significant increases (red spectrum) or decreases (blue spectrum) in HG energy relative to pre-cue baseline in 16-ms windows. Each row corresponds to a different electrode as displayed on the right brain maps. All times are relative to cue onset ($t = 0$ s). To highlight the spatial pattern of cortical activation at early (visual/auditory perception) and late (response production) stages, HG responses are integrated across an early and late temporal window (early stage highlighted in blue and late stage in red on raster plot), and shown in separate brain maps (early stage in the top brain and late stage in the bottom brain). Microelectrode arrays AMIC and PMIC are enlarged for better visualization of HG responses. The early and late stages can be modified by the user offline, based on the spatial-temporal evolution observed in the raster, to visualize the spatial distribution of activation during different observed task stages. In this illustration, the early sections were chosen to map perceptual processing stages and the late sections were chosen to map response production. Early and late sections in this figure were chosen manually and the integrated brain map was generated post hoc. Second brain image and highlighting of early and late time periods on the channel raster have been added to the screenshot post hoc (i.e., they are not available online). Red: tongue/mouth motor; blue: tongue/mouth sensory; purple: picture naming (A), language comprehension (B); pink: spontaneous speech (B); light green: clear for tongue/mouth motor/sensory; dark green: clear for picture naming (A), clear for language comprehension/spontaneous speech (B).

Figure 2 Visual object naming task and auditory word repetition task results for patients 2-7

A. Visual object naming

B. Auditory word repetition

(A) Visual object naming task and (B) auditory word repetition task. Electroocut stimulation mapping (ESM) and online spatial-temporal functional mapping (STFM) results are overlaid on brain maps with highlighted regions of interest (ROIs). As in figure 1, online results are separated into early stage (visual perception, left brain) and late stage (response production, right brain), where high-gamma (HG) responses were computed by integrating across an early or late temporal interval. Microelectrode arrays are enlarged for better visualization. Red: tongue/mouth motor; blue: right upper quadrant vision (P2);

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(2.3 mm diameter). One might expect that task-related cortical activation at this scale would be highly correlated among adjacent microelectrodes, resulting in highly uniform spatial-temporal patterns of activation. However, in many instances we observed a surprising degree of heterogeneity in the temporal and spatial patterns of activation at different microelectrodes within individual micro-ECoG arrays.

ECoG maps vs electrical stimulation maps. STFM results for both visual object naming and auditory word repetition tasks for each patient were first computed by using ESM results as the gold standard (table 1). The average sensitivity across tasks and patients was 69.9%, and the average specificity was 83.5%. Table 2 shows STFM vs ESM test results for both ROI+ and ROI− stimulation sites across all patients.

The sensitivity and specificity of both ESM and STFM using anatomical ROIs as a gold standard were calculated across patients, using equations 2.1–2.4 and values from table 2. The average sensitivity across tasks and patients was 65.6% for STFM vs 47.9% for ESM; the overall average specificity was 86.2% for STFM vs 78.0% for ESM. The sensitivity of STFM was significantly greater than that of ESM ($p = 0.0068$, McNemar test), while the specificity of STFM appeared to be greater than that of ESM, but this difference was not statistically significant ($p = 0.066$, McNemar test).

DISCUSSION Results from 7 patients demonstrated that our online STFM system is fast and robust enough to compute cortical maps of language function for online review, using ECoG HG responses that correspond well to ESM results.

The time-consuming and taxing nature of ESM motivates the development of a passive functional mapping alternative. Online STFM based on event-related changes in ECoG signals provides important opportunities for clinicians. The clinical utility of STFM currently lies in both augmenting the findings from ESM and identifying the areas of potential functional significance as a guide to further exploration by ESM. STFM has the advantage of being performed at all recording sites simultaneously. Additionally, it can provide a graded measure of cortical activation that allows clinicians to estimate the relative contribution of different cortical sites to task performance.

With a larger body of evidence, it may be possible to someday make clinical decisions from passive functional mapping alone. Mapping language cortex

presents challenges, however, since multiple sites over large-scale cortical networks are involved. Although some studies have indicated poor sensitivity and specificity of ECoG mapping in relation to ESM (e.g., specificity of 78% and sensitivity of 38% during visual object naming¹²), recent reports have suggested that in some instances it can be more predictive of postoperative language impairments than ESM.^{10,26,27} More work will be required to correlate surgical outcomes with the location of resected and preserved sites identified by ESM and STFM.

Compared to existing ECoG functional mapping systems, our STFM system offers several key advantages. First, our trial-based system constructs a baseline distribution from the pre-cue phases of individual trials, rather than a pre-session block of baseline activity, as employed by previous studies.^{15,28} The pre-cue baseline provides the best control for active periods because it controls for variations in the arousal and attentiveness of the patient that are not directly related to testing. Trial-based analyses also provide greater cognitive control during both the baseline and the active period than do block-based designs. In a block design, it is difficult to ensure that a patient is continuously performing a task during a long active period without contaminating this period with unintended cognitive events or brief rest periods. Behavioral responses can also be used to trigger the STFM system, but variable response latencies and artifacts in speech onset detection can be challenging, particularly when implemented online.

Previous studies of ECoG mapping using the HG frequency band have shown comparable, if slightly lower, sensitivities and specificities relative to ESM (table e-2).^{18–21} These studies have all assumed ESM as the gold standard for identifying eloquent cortex and predicting postresection deficits. The ideal gold standard for functional mapping is postoperative outcome following resection of a cortical site. However, this is difficult to achieve in clinical practice because resections always include more than one site and because reorganization of function inevitably takes place following resection such that deficits appearing immediately after surgery often resolve. To demonstrate superiority over ESM, ECoG would have to make better predictions of these deficits, as well as more persistent deficits, preferably in a prospective cohort of patients.

Concerns about the accuracy of ESM can be traced back to its inception in clinical practice.^{29,30} It has long been recognized that cortical stimulation can affect function at a distance,⁷ and that ESM does

Figure 2 legend, continued:

visual sensory (P4), tongue/mouth sensory (P6, P7); purple: picture naming (P2, P3, P4, P5, P7 in A), language comprehension (P4 in B); pink: spontaneous speech (P2, P3, P4, P7 in B); light green: clear for picture naming and motor function (P2, P3, P4 in A), clear for spontaneous speech/language comprehension and motor function (P2, P3, P4, P5, P6 in B), clear for motor function (P7 in B); dark green: clear for spontaneous speech/language comprehension (P7 in B).

Figure 3 Single trial responses from online spatial-temporal functional mapping (STFM) results for patient 1, auditory word repetition task

The single trial activations are shown for the auditory word repetition task in 3 separate electrodes: (A) LFT23, a macroelectrode in the early responding, putative stimulus perception cluster; (B) LFT45, a macroelectrode in the late responding, putative verbal response cluster; and (C) PMIC13, a microelectrode from the late responding cluster. The colors shown are scaled according to the negative log of the *p* value, computed as a series of *t* tests with the channel baseline distributions at the time of the trial. Significance thresholds have not been false discovery rate (FDR)-corrected for multiple comparisons, as the single trial responses are primarily intended as an indicator of neural response consistency across trials. Each trial raster has a row at the bottom with the FDR-corrected estimate of trial-averaged activation (identically displayed on the channel raster, figure 1).

not always predict postoperative language outcomes.^{10,26,31} This concern is perhaps best illustrated in somatosensory and motor cortices, where the effects of lesions are more predictable. Although stimulation of postcentral gyrus often elicits motor responses, resection of this gyrus causes sensory impairments and apraxia, but not weakness per se.^{30,32}

Conversely, stimulation of precentral gyrus can elicit somatic sensations. Indeed, clinical investigators have elicited movements with stimulation 1.5–4.7 cm anterior and 2–3.4 cm posterior to the central sulcus, but resection of most of this territory can be performed with little or no motor impairment.^{30,32} Indirect evidence for distant effects of ESM can also be found in studies where direct cortical stimulation has elicited both evoked responses³³ and HG responses³⁴ in distant cortical regions that have putative functional connectivity with the stimulation site. Because HG responses reflect population firing rates,^{35,36} the latter study suggests that ESM can affect neuronal firing in distant populations, though the effect on cortical function is unknown.

Because of the potential limitations of ESM for functional localization, is important to evaluate the accuracy of both ECoG and ESM with respect to an independent measure of cortical function. This can be drawn from the rich literature on the effects of discrete brain lesions,^{37,38} as well as on regions typically activated on fMRI during experimental language tasks, albeit at far lower temporal resolution.^{37,39,40} Using this approach, we found that the sensitivity of STFM was significantly greater than that of ESM, while the specificity of STFM was greater than that of ESM, though not significantly so. In

Table 1 Sensitivity and specificity values for STFM during visual object naming and auditory word repetition tasks, with ESM as the gold standard

Comparison of STFM vs ESM				
Patient no.	Visual object naming		Auditory word repetition	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
1	100.0	94.4	100.0	78.6
2	33.3	69.2	100.0	78.6
3	75.0	62.5	100.0	77.8
4	85.7	65.0	28.6	92.9
5	100.0	90.0	100.0	100.0
6	0.0	90.3	50.0	90.3
7	50.0	92.3	55.6	86.7
Average	63.4	80.5	76.3	86.4

Abbreviations: ESM = electrocortical stimulation mapping; STFM = spatial-temporal functional mapping.

Table 2 STFM vs ESM test results among ROI+ and ROI– stimulation sites, across all patients

	ROI+ stimulation sites			ROI– stimulation sites		
	STFM+	STFM–	Row total	STFM+	STFM–	Row total
ESM+	37	9	46	10	17	27
ESM–	26	24	50	7	89	96
Column total	63	33	96	17	106	123

Abbreviations: ESM = electrocortical stimulation mapping; ROI = region of interest; STFM = spatial-temporal functional mapping.

light of these findings, both ESM and passive ECoG mapping offer approximations of the patient's true functional anatomy and more studies are needed to understand their comparative utilities in clinical practice.

We have demonstrated a system that is able to compute spatial-temporal functional maps online, allowing for immediate access to ECoG mapping results at the patient's bedside. Our approach is generalizable to a variety of clinical and experimental applications. For example, this system could easily be adapted to the time-pressured circumstances of an awake craniotomy. This information can help clinicians better understand the contributions that tested sites make to task performance and help avoid cortical areas critical to eloquent function during surgical planning.

AUTHOR CONTRIBUTIONS

Y. Wang: study concept and design, acquisition of data, analysis and interpretation, manuscript write-up. Dr. Fifer: study concept and design, acquisition of data, analysis and interpretation, manuscript write-up. Dr. Flinker: study concept, manuscript revision. Dr. Korzeniewska: study concept, manuscript revision. Dr. Cervenka: acquisition of data. Dr. Anderson: acquisition of data. Dr. Boatman-Reich: acquisition of data, manuscript revision. Dr. Crone: study concept, acquisition of data, analysis and interpretation, manuscript write-up, study supervision.

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