Melinda Wu, BS
Washington University School of Medicine,
Washington University in St. Louis,
St. Louis, Missouri

Kimberly Wisneski, MS
Department of Biomedical Engineering,
Washington University in St. Louis,
St. Louis, Missouri

Gerwin Schalk, PhD
Department of Neurological Surgery,
Washington University School of Medicine,
St. Louis, Missouri;
Department of Neurology,
Albany Medical College,
Albany, New York;
Department of Biomedical Engineering,
Rensselaer Polytechnic Institute,
Troy, New York;
Department of Biomedical Science,
State University of New York at Albany,
Albany, New York; and
BCI R&D Program,
Wadsworth Center,
New York State Department of Health,
Albany, New York

Mohit Sharma, BS
Department of Biomedical Engineering,
Washington University in St. Louis,
St. Louis, Missouri

Jarod Roland, BS
Washington University School of Medicine,
Washington University in St. Louis,
St. Louis, Missouri

Jonathan Breshears, BS
Washington University School of Medicine,
Washington University in St. Louis,
St. Louis, Missouri

Charles Gaona, MS
Department of Biomedical Engineering,
Washington University in St. Louis,
St. Louis, Missouri

Eric C. Leuthardt, MD
Department of Biomedical Engineering,
Washington University in St. Louis, and
Department of Neurological Surgery,
Washington University School of Medicine,
St. Louis, Missouri

Reprint requests:
Eric C. Leuthardt, MD,
Washington University School of Medicine,
Department of Neurological Surgery,
660 S Euclid Ave,
Campus Box 8057,
St Louis, MO 63110.
E-mail: leuthardte@nsurg.wustl.edu

Received, February 8, 2009.
Accepted, August 11, 2009.

Electrocorticographic Frequency Alteration Mapping for Extraoperative Localization of Speech Cortex

OBJECTIVE: Electrocortical stimulation (ECS) has long been established for delineating eloquent cortex in extraoperative mapping. However, ECS is still coarse and inefficient in delineating regions of functional cortex and can be hampered by afterdischarges. Given these constraints, an adjunct approach to defining motor cortex is the use of electrocorticographic (ECoG) signal changes associated with active regions of cortex. The broad range of frequency oscillations are categorized into 2 main groups with respect to sensorimotor cortex: low-frequency bands (LFBs) and high-frequency bands (HFBs). The LFBs tend to show a power reduction, whereas the HFBs show power increases with cortical activation. These power changes associated with activated cortex could potentially provide a powerful tool in delineating areas of speech cortex. We explore ECoG signal alterations as they occur with activated region of speech cortex and its potential in clinical brain mapping applications.

METHODS: We evaluated 7 patients who underwent invasive monitoring for seizure localization. Each had extraoperative ECS mapping to identify speech cortex. Additionally, all subjects performed overt speech tasks with an auditory or a visual cue to identify associated frequency power changes in regard to location and degree of concordance with ECS results.

RESULTS: Electrocorticographic frequency alteration mapping (EFAM) had an 83.9% sensitivity and a 40.4% specificity in identifying any language site when considering both frequency bands and both stimulus cues. Electrocorticographic frequency alteration mapping was more sensitive in identifying the Wernicke area (100%) than the Broca area (72.2%). The HFB is uniquely suited to identifying the Wernicke area, whereas a combination of the HFB and LFB is important for Broca localization.

CONCLUSION: The concordance between stimulation and spectral power changes demonstrates the possible utility of EFAM as an adjunct method to improve the efficiency and resolution of identifying speech cortex.

KEY WORDS: Brain mapping, Electrocorticography, Speech cortex

Neurosurgery 66:E407-E409, 2010 DOI: 10.1227/01.NEU.0000345352.13696.6F www.neurosurgery-online.com

The practice of mapping eloquent cortex in the extraoperative setting before resection in neurologic surgeries has been important in reducing the risk of morbidity after surgery.[1-3] This is particularly true in surgical resection for the treatment of medically intractable epilepsy where patients require placement of subdural arrays for seizure localization.[1,2] Because of the interindividual variability in the anatomical location of language areas, the mapping of these speech areas is especially critical.[1,4,5] Electrocortical stimulation (ECS) is the current "gold standard" for clinical mapping. This methodology, however, has several important limitations. Electrocortical stimulation mapping can be hampered by the induction of afterdischarges that can induce seizures and introduce a source of error in mapping. Blume et al[6] reported that 71% of patients experienced afterdischarges during ECS mapping. The study also demonstrated that 65% of afterdischarges involved more than 1 electrode, which could potentially interfere with accurate mapping.[6] Additionally, ECS can be associated with pain on stimulation, which may further hin-

ABBREVIATIONS: ECoG, electrocorticography; **ECS**, electrocortical stimulation; **EEG**, electroencephalography; **EFAM**, electrocorticographic frequency alteration mapping; **HFB**, high-frequency band; **LFB**, low-frequency band der effective localization.[7,8] Although effective in identifying important regions of functional cortex, ECS is relatively inefficient: sites must be interrogated in series (ie, pairs of electrodes are sequentially stimulated while patients perform various tasks), resulting in a prolonged screening process. For these reasons, it is desirable to improve the efficiency and accuracy of cortical mapping by supplementing ECS with another method of mapping. An alternate method would be important in cases in which pain or afterdischarges prohibit ECS mapping altogether. One possibility is the use of passively recorded cortical changes in activity associated with a given cognitive task, a method known as electrocorticographic frequency alteration mapping (EFAM).[9]

Electrocorticography (ECoG) records electrical activity generated by the brain from subdural electrodes placed directly on the cortical surface. These electrode arrays are typically implanted for the dual purpose of localizing seizure activity and for extraoperative cortical stimulation mapping of functional regions. Like electroencephalography (EEG), which records electrical activity from the scalp, ECoG records oscillations in the mu (8-12 Hz) and beta (18-26 Hz) frequency bands. These bands have been shown to decrease in amplitude in relation to various cognitive tasks.[9-13] The lower-frequency mu and beta bands are thought to represent activity from thalamocortical circuits, which may be suppressed during cortical activation. In addition, unlike EEG recordings, ECoG recordings include task-related signals in the higher gamma frequency range (> 30 Hz). These high frequencies show an increase in amplitude in association with numerous motor, language, and cognitive tasks.[9-11,14-16] Gamma changes are thought to represent the cortical activity from smaller cortical assemblies of neurons involved in task performance.[13,17] Both low- and high-frequency amplitude changes have been shown to localize topographically over areas of active cortex.[8,9,11,14,15]

Electrocorticography has been used to study the cortical physiology of motor and language function by multiple investigators.[8,9,11,14] Crone et al[11] showed mu and beta rhythms to have a reduced amplitude (termed event-related desynchronization) and gamma rhythms to have an increased amplitude with voluntary movement (termed *event-related synchronization*). Crone et al[11] found changes associated with gamma activity to have a more localized topographic pattern and concluded that these rhythms were potentially more useful for mapping. In addition, the cortical area over which gamma changes occurred corresponded better to traditional somatotopic locations of motor cortex and ECS maps. Crone et al[10] performed a similar analysis with speech and again found broad suppression of the lower frequencies and a more focal augmentation of the higher-frequency gamma rhythms.

Recent studies have attempted to further define the utility of these cortical frequency alterations (ie, EFAM) in mapping eloquent areas of cortex. Leuthardt et al[15] compared motor cortical activation maps generated by EFAM analysis with ECS mapping of the same motor areas. Sites associated with high-frequency changes were found to be more specific, whereas sites associated with low-frequency changes were found to be more sensitive in identifying functional motor cortex defined by ECS. These more passive techniques of identifying functional cortex have also been extended to localization of speech. Because language is more complex than movement and requires the coordinated activity of multiple cortical areas, several experimental paradigms have been explored. Based on the initial findings of Crone et al of a more discrete gamma augmentation with auditory perception, later studies of ECoG mapping of language areas focused solely on gamma event-related synchronization. The first of these investigated the pattern of gamma activation during various language tasks—picture naming, word reading, and word repetition—with both spoken and signed output, in a patient fluent in both spoken and sign language.[15] In this study, an overlap between ECoG- and ECS-identified areas of activation was noted. A later study focused on the potential use of ECoG for mapping during a picture-naming task in multiple subjects.[8] When compared with ECS, gamma activations were found to have low sensitivity and high specificity for identifying sites associated with stimulation-induced language disruption. However, a recent study of auditory language in children showed the opposite effect: that gamma activation occurred over a larger area of cortex than that identified by ECS.[14]

In the current study, the utility of EFAM for identification of language sites was investigated. Previously mentioned studies and others[18,19] indicate that different cortical areas are activated when different language modalities are used. Additionally, passive mapping has focused primarily on gamma rhythms as the signal important for mapping. Thus far, the modality and frequency bands have not been studied together to assess what provides the best or most useful information for localization. The goal of this work was to identify the role different language modalities and different frequency rhythms play in identifying cortical regions involved with speech. To do this, the sensitivity and specificity of EFAM to identify sites localized with cortical stimulation were defined generally, according to whether they were receptive or expressive speech sites, which stimulus was provided, and by what frequency band (low or high) best identified a given speech site. Generally, we find both cue modality and frequency band play an important role when attempting to identify either receptive or expressive speech sites with stimulation. Taken together, these findings support the use of EFAM with multimodal cues as a safe and efficient supplement to electrocortical stimulation for the purposes of extraoperative functional localization of speech.

PATIENTS AND METHODS

To test the efficacy of the EFAM approach for speech localization, we evaluated 7 patients with medically intractable epilepsy in whom subdural grid electrodes were placed for the purpose of extraoperative ECoG recording for seizure localization. The grid electrodes were also used for extraoperative electrocortical stimulation mapping of language areas. In addition, ECoG recordings were obtained while subjects performed overt speech tasks cued with either auditory or visual stimuli. Electrocorticographic recordings were analyzed to determine the location of significant amplitude changes in both low- and high-frequency bands during the speech tasks. The results of these analyses were then compared with the results of electrical stimulation mapping.

Patients

Study participants were 7 patients (5 male and 2 female) who underwent surgical resection for the treatment of intractable epilepsy at Washington University in St. Louis. Patients were aged 14 to 58 years, and all had cognitive capacity in the normal range. Grids were placed on the left hemisphere and covered putative language areas (Table 1). Recording lasted 3 to 11 days, and all experiments and electrical stimulation mapping occurred extraoperatively using these grids. The study was approved by the Human Research Protection Office at Washington University in St. Louis.

Experimental Setup

Patients were seated 75 to 100 cm away from a standard flat-screen monitor on which visual stimuli were presented and wore earplug headphones for auditory stimuli. Visual and auditory cues were presented using the BCI2000 program.[20] BCI2000 is a general-purpose system for data acquisition, stimulus presentation, and brain monitoring. In the context of brain mapping, it supports programmable presentation of auditory/visual stimuli and simultaneous ECoG signal recordings. BCI2000 associates the timing of these stimuli with the recorded ECoG signals, which facilitates offline analyses. The signal from the patient's subdural electrode grid array was split via a custom Ad-Tech (Racine, Wisconsin) cable that sent signals to both the clinical network for epilepsy monitoring and a separate U.S. Food and Drug Administration–approved amplifier/digitizer system (g.tec Guger Technologies, Graz, Austria) that was connected to an acquisition computer running BCI2000. Electrodes were referenced to an inactive intracranial electrode, amplified, band-pass filtered (0.15-500 Hz), digitized at 1200 Hz, and stored. Electrode grids consisted of 64 circular platinum electrodes 4 mm in diameter, with 2.3 mm exposed, and spaced 10 mm apart from center to center. Electrodes were arranged in an 8 × 8 grid and embedded in silastic sheets 80 × 80 mm in size, manufactured by Ad-Tech. We recorded from all 64 grid electrodes in 6 of 7 patients and from a subset of 16 electrodes in the remaining patient.

Stimuli

In the experimental paradigm, subjects received 1 of 2 types of verbal stimuli: auditory and visual. The subjects performed 2 sessions of simple verbal tasks. The first session was a visual session, in which the subject saw a word presented on the screen and was instructed to speak the word. The second task was the auditory session, in which the subject heard the word and was instructed to repeat it. Each session consisted of 4 phonemic classes of words (*ee*, *eh*, *ah*, and *oo*) that were consonant matched (eg, *heed*, *head*, *had*, *hood*). Each session consisted of 3 to 6 runs (3 min each) with a 1-minute break in between. Each run consisted of 36 words, which were randomly presented for 4 seconds. The total time for both sessions was 24 to 48 minutes, depending on the patient's willingness to participate.

TABLE 1. Clinical summary of patients involved in the study

Patient No.	Age (y)/Sex	Hand	Cognitive Capacity	Grid Location	Seizure Focus
1	44/F	L	Normal	L frontal temporal parietal	L temporal
2	15/F	R	Normal	L frontal temporal	L temporal
3	14/M	R	Normal[a]	L frontal parietal	L frontal
4	43/M	R	Normal	L frontal temporal	L orbitofrontal
5	48/F	L	Normal	L frontal temporal parietal	L temporal
6	58/F	R	Normal	L frontal	L frontal
7	49/F	R	Normal	L frontal temporal parietal	L temporal

[a] Nonverbal learning disorder.

Analysis

Electrocorticographic data from each 4-second trial were analyzed. First, we excluded channels that did not obviously contain ECoG activity, such as those containing artifacts because of broken connections. Then, the signal from each remaining channel was referenced to the signal mean from all channels. Subsequently, for each 500-millisecond time period (overlapping by 250 milliseconds), we converted the time series ECoG data into the frequency domain with an autoregressive model[21] of order 25. Using this model, we calculated spectral amplitudes between 0 and 200 Hz in 1-Hz bins. We averaged these spectral amplitudes in particular frequency ranges as follows:

1) 8 to 32 Hz (low-frequency band [LFB]): This range covers the classic mu/beta band associated with movements and other tasks.
2) 75 to 100 Hz (high-frequency band [HFB]): This particular interval was chosen because it lies within the broad gamma band frequency power increase and was distant from possible contamination from line noise (at 60 Hz and its first harmonic, ie, 120 Hz).

For each electrode, we compared the distribution of amplitudes in the HFB and LFB bands for each stimulus modality (auditory and visual) versus the corresponding distribution during rest intervals. To do this, we calculated the coefficient of determination, or r^2 value, of the amplitude change with the given speech task when compared against rest. The r^2 indicates how much variance in the amplitudes corresponds to a given condition. Thus, if the amplitude increased in the HFB every time the speech task was performed, the coefficient of determination would be 1 ($r^2 = 1$). If the amplitude increased only some of the time the speech task was performed, the coefficient of determination (r^2) would be reduced but larger than 0. Therefore, the r^2 value associated with each electrode and LFB/HFB frequency band was always positive. Separately, a P value was also calculated using a balanced, 1-way analysis of variance with these same HFB and LFB power alterations. Only electrodes with changes with a P value less than .05 were considered significant and used for further analysis for localization and visualization of signal change and comparison with ECS-identified electrodes.

Anatomical Localization of Signal Change

X-rays were used to identify the stereotactic coordinates of each grid electrode,[22] and cortical areas were defined using *Talairach's Co-Planar Stereotaxic Atlas of the Human Brain*[23] and a Talairach transformation database.[24] We obtained a template 3-dimensional cortical brain model from the AFNI SUMA Web site.[25] Stereotactically defined electrode locations were then mapped to this template brain model. Next, we created r^2 activation plots for each stimulus modality and both the HFB and LFB for each patient using a customized MatLab (The MathWorks, Inc, Natick, Massachusetts) program. For each plot, only electrodes with a P value of less than .05 were considered. The resulting map showed the activation at each point on the brain model for the condition and frequency band analyzed. For comparison, language-related electrodes identified by electrical stimulation mapping were shown on the same plots using the stereotactically defined electrode locations described previously.

Electrocortical Stimulation Mapping

All patients underwent extraoperative electrocortical stimulation to identify areas of eloquent cortex, including language areas. This procedure was separate from the experiments reported previously and was performed solely for clinical purposes. Stimulation at 40 Hz with a pulse width of 500 microseconds was passed through paired electrodes for 2 seconds. Current was progressively increased from 1 mA up to 10 mA, or until afterdischarge threshold was reached, while the patients performed different language tasks. An electrode was considered positive for language if a language error occurred during stimulation. Electrocortical stimulation–positive electrodes were highlighted on the maps described previously.

Comparison of ECS and EFAM Maps

For each individual subject, electrodes that were positive for speech during ECS mapping were identified and compared with electrodes that showed a significant ($P < .05$) change in power during ECoG recording while the subject performed language tasks. Expressive (Broca) and receptive (Wernicke) speech areas were analyzed both separately and together. Tasks performed with auditory and visual inputs were analyzed both separately and together. Finally, significant electrodes identified in the LFB and HFB were also analyzed both separately and together.

For each of these analyses, a sensitivity and specificity analysis was performed to evaluate the ability of EFAM to predict ECS-positive language sites (the true-positive sites). The sensitivity was calculated as the number of true positives (both EFAM- and ECS-positive electrodes) divided by the total number of ECS-positive electrodes (including both true positives and false negatives—ECS-positive electrodes that EFAM did not identify). The specificity was calculated as the number of true negatives (both EFAM- and ECS-negative electrodes) divided by the total number of ECS-negative electrodes (including both true negatives and false positives—ECS-negative electrodes that EFAM incorrectly identified). An example is shown below (see Table 2 for determining sensitivity and specificity):

Low-frequency band sensitivity and specificity for Broca area visual condition:

Sensitivity = 6/(6 + 12) = 0.333 = 33.3%

Specificity = 204/(52 + 204) = 0.797 = 79.7%

A χ^2 analysis was performed to assess the statistical probability of rejecting the null hypothesis of independence of ECS- and EFAM-generated maps of language areas. In a previous study of the usefulness of EFAM in mapping motor cortex, electrodes were assessed both individually and in nonoverlapping pairs.[9] We chose to forgo the pairs analysis in this study because not all study patients underwent ECS mapping using nonoverlapping pairs.

TABLE 2. Determination of sensitivity and specificity[a]

	True +	True
Test +	A	B
Test	C	D
	ECS +	ECS
LFB +	6	52

[a] ECS, electrocortical stimulation; LFB, low-frequency band.
Sensitivity = A/A + C; specificity = D/B + D

In our final method of analysis, EFAM and ECS mapping were compared by projecting the results of both methods onto a standardized brain model. This allowed us to qualitatively compare the location and distribution of the language-associated electrodes identified by EFAM and ECS. Additionally, this method enabled us to inspect the degree of consistency in power change associated with each electrode for each task.

RESULTS

We correlated the results of ECS and EFAM mapping in several ways. To determine whether different input modalities activate different language areas, we assessed the results of the 2 conditions, auditory and visual stimulus presentation, both separately and together. For each condition, we analyzed Broca (expressive speech) and Wernicke (receptive speech) areas individually and collectively. Of the 7 patients in this study, 6 subjects had ECS-positive electrodes for expressive speech, and 4 subjects had ECS-positive electrodes for receptive speech. Each correlation considered the EFAM data from the LFB, HFB, and both LFB and HFB taken together (EFAM positive). Electrodes were considered to be EFAM positive if they demonstrated significant signal alteration in the LFB, HFB, or both. The absolute number of electrodes studied, their functional responses, and the sensitivity and specificity of the EFAM method are summarized in Tables 3 and 4.

When we calculated the sensitivity and specificity of EFAM compared with ECS mapping of language areas in the auditory condition, LFB was 44.4% sensitive and 67.2% specific for identifying the Broca area, 23.1% sensitive and 89.4% specific for identifying the Wernicke area, and 35.5% sensitive and 74.0% specific for identifying either the Broca or the Wernicke area; HFB was 44.4% sensitive and 66.0% specific for the Broca area, 61.5% sensitive and 75.2% specific for the Wernicke area, and 51.6% sensitive and 68.8% specific for the Broca or Wernicke area. In the visual condition, LFB was 33.3% sensitive and 79.7% specific for the Broca area, 38.5% sensitive and 87.6% specific for the Wernicke area, and 35.5% sensitive and 82.1% specific for the Broca or Wernicke area; HFB was 27.8% sensitive and 75.4% specific for the Broca area, 84.6% sensitive and 82.3% specific for The Wernicke area, and 51.6% sensitive and 77.5% specific for the Broca or Wernicke area.

When considering both the auditory and visual conditions together, LFB was 55.6% sensitive and 57.8% specific for the Broca area, 38.5% sensitive and 79.6% specific for the Wernicke area, and 48.4% sensitive and 64.5% specific for the Broca or Wernicke area; HFB was 50% sensitive and 57.4% specific for the Broca area, 100% sensitive and 65.5% specific for the Wernicke area, and 71% sensitive and 59.9% specific for the Broca or Wernicke area.

Assessing the correlation of EFAM-positive sites (electrodes with significant LFB or HFB signal alteration or both) compared with ECS-positive sites generally resulted in a higher sensitivity and lower specificity than the same calculations using either the LFB or the HFB alone. In the auditory condition, EFAM-positive sites were 66.7% sensitive and 46.5% specific for the Broca area,

TABLE 3. Electrode summary[a]

Electrode Summary	Stimulus Auditory	 Visual
Total number of electrodes	400	400
Electrodes with significant LFB power change during speech	107	77
Electrodes with significant HFB power change during speech	131	99
Electrodes with either significant LFB or HFB power change during speech (EFAM+)	192	143
Electrodes producing speech response with stimulation	31	31
Electrodes with significant LFB power change and speech response with stimulation	11	11
Electrodes with significant HFB power change and speech response with stimulation	16	16
Electrodes with either significant LFB or HFB power change and speech response with stimulation	21	19

[a] LFB, low-frequency band; HFB, high-frequency band; EFAM, electrocorticographic frequency alteration mapping. Compilation of data involving speech localization with electrocortical stimulation–associated speech findings and significant LFB and HFB power change ($P < .05$). The numbers given are summed across all patients.

TABLE 4. Summary of statistical analysis[a]

Stimulus	Broca Area		Wernicke Area		Broca and Wernicke Areas	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Auditory						
LFB	44.4	67.2	23.1	89.4	35.5	74.0
HFB	44.4	66.0	61.5	75.2	51.6	68.8
EFAM+	66.7	46.5	69.2	69.9	67.7	53.7
Visual						
LFB	33.3	79.7	38.5	87.6	35.5	82.1
HFB	27.8	75.4	84.6	82.3	51.6	77.5
EFAM+	44.4	63.7	84.6	72.6	61.3	66.4
Auditory and visual						
LFB	55.6	57.8	38.5	79.6	48.4	64.5
HFB	50.0	57.4	100.0	65.5	71.0	59.9
EFAM+	72.2	34.0	100.0	56.6	83.9	40.4

[a] LFB, low-frequency band; HFB, high-frequency band; EFAM, electrocorticographic frequency alteration mapping. Summary of the LFBs, HFBs, and LFB and/or HFB (EFAM+) signal alteration in detecting electrocortical stimulation–positive electrodes for induced speech errors or arrest. Data are percentages.

69.2% sensitive and 69.9% specific for the Wernicke area, and 67.7% sensitive and 53.7% specific for the Broca or Wernicke area. In the visual condition, EFAM-positive sites were 44.4% sensitive and 63.7% specific for the Broca area, 84.6% sensitive and 72.6% specific for the Wernicke area, and 61.3% sensitive and 66.4% specific for the Broca or Wernicke area. When EFAM-positive sites in both the auditory and the visual condition were compared with ECS-positive sites, sensitivity was 72.2% and specificity was 34% for identifying the Broca area; for the Wernicke area, sensitivity was 100% and specificity was 56.6%; and for the Broca or Wernicke area, sensitivity was 83.9% and specificity was 40.4% (Table 4).

The χ^2 test was used to determine whether the distribution of electrodes identified by EFAM mapping significantly overlapped with the corresponding electrodes from ECS mapping. Statistically significant overlap at the $P < .05$ level was found for the Wernicke area during auditory stimulation when HFB was considered alone or together with LFB, during visual stimulation in all frequency band categories (LFB, HFB, and LFB and HFB combined), and in the combined auditory and visual conditions when HFB was considered alone or together with LFB. When both the Broca and Wernicke areas were considered, statistically significant overlap was found during the auditory stimulation when HFB was considered alone or together with LFB, during visual stimulation, in all frequency band categories, and in the combined auditory and visual conditions when HFB was considered alone or together with LFB.

Figures 1 through 4 demonstrate for each subject the grid electrodes and the regions of cortex identified on the template brain

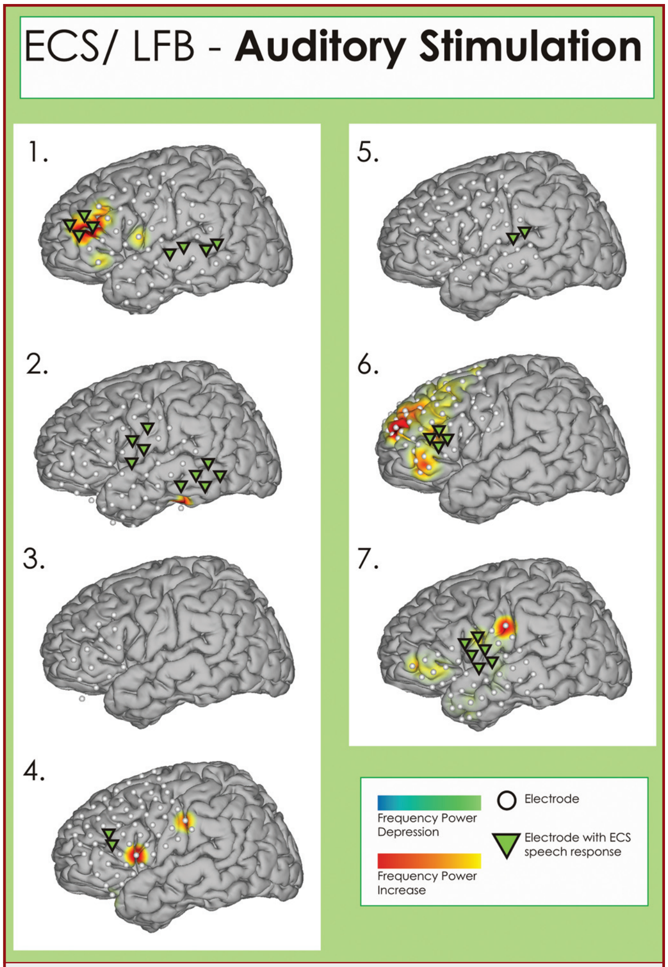

FIGURE 1. *Comparison of stimulation mapping and low-frequency band (LFB) power alteration for auditory cued speech task. The figure shows, for patients 1 to 7, the grid electrodes and the regions of cortex identified on the template brain which demonstrate significant LFB power alteration in context to the electrodes that induced speech errors/arrest with electrocortical stimulation (ECS). The values are normalized to maximum increase or decrease, such that an activation of 0 is always gray, with maximum increase as red, and maximum decrease as blue, scaled to whatever the highest absolute value in the activation map is. Maps that appear purely gray had no significant change with the stated motor modality. Electrode locations are shown as white dots. Electrodes where clinical stimulation produced a speech effect of the type being mapped are shown with green triangles. In general, auditory cued speech induced cortical power changes in the LFB which correlated with regions identified with ECS more notably in the frontal lobe. Patient 3 did not show sites detectable with ECS.*

that demonstrate significant power alteration with respect to the LFB or the HFB in context to either auditory or visual stimuli. In general, both visual and auditory stimuli for speech induced power changes in the LFB and HFB. The cortical topographical distribution for the significant LFB and HFB power changes were both focal, but tended to be anatomically distinct. Low-frequency band changes tended to be more localized to the frontal lobe, whereas HFB changes tended to be more localized to the temporal lobe. Additionally, the cortical distribution of the power change in both frequency bands was different between the stimulation modalities.

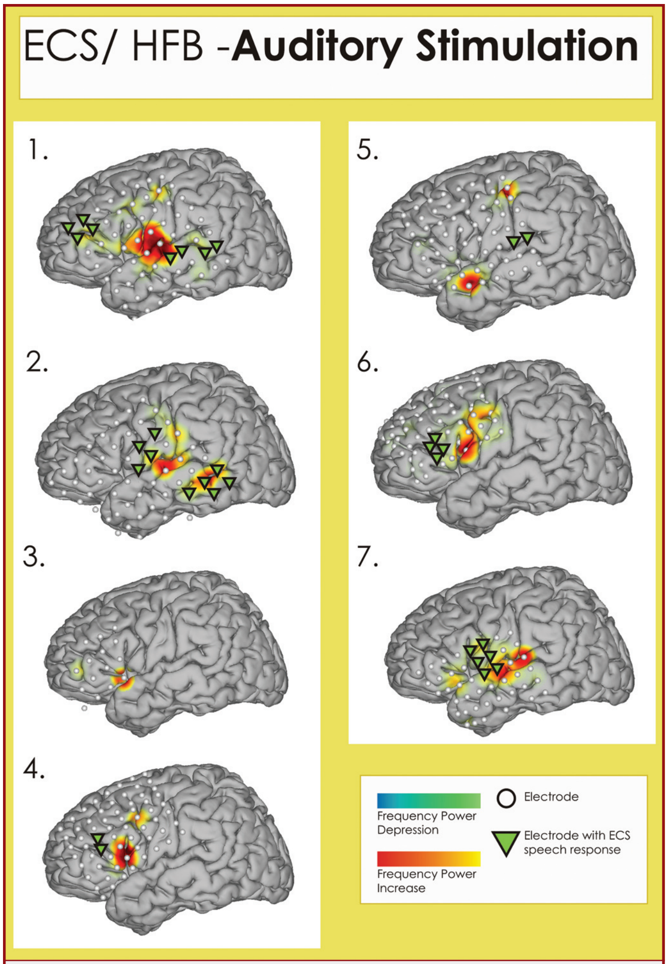

FIGURE 2. *Comparison of stimulation mapping and high-frequency band (HFB) power alteration for auditory cued speech task. The figure shows, for patients 1 to 7, the grid electrodes and the regions of cortex identified on the template brain which demonstrate significant HFB power alteration in context to the electrodes that induced speech errors/arrest with electrocortical stimulation (ECS). In general, auditory cued speech induced a more focal region of cortical power increase in the HFB which correlated more closely with regions identified with ECS. Patient 3 did not show sites detectable with ECS.*

DISCUSSION

The results of this study demonstrate the technical feasibility of EFAM and show it can potentially be used as an adjunct to identify language cortex. To summarize, in comparison with ECS, the gold standard for cortical mapping, EFAM had an 83.9% sensitivity and a 40.4% specificity in identifying any language site, when both frequency bands (LFB + HFB) and both stimulus cues (auditory and visual) were considered. In general, EFAM tended

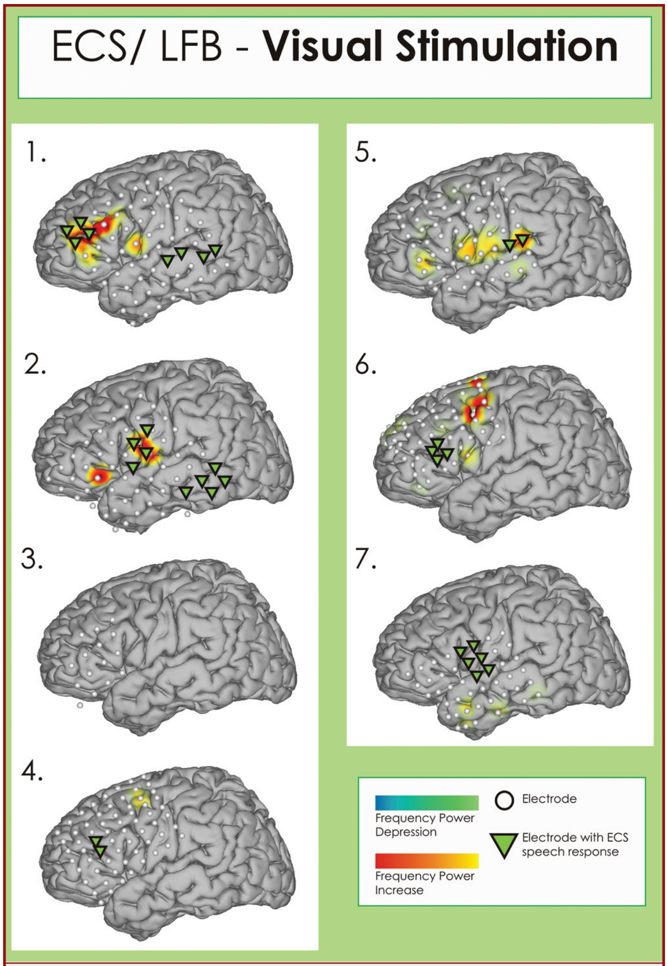

FIGURE 3. *Comparison of stimulation mapping and low-frequency band (LFB) power alteration for visual cued speech task. The figure shows, for patients 1 to 7, the grid electrodes and the regions of cortex identified on the template brain which demonstrate significant LFB power alteration in context to the electrodes that induced speech error/arrest with electrocortical stimulation (ECS). In general, visually cued speech induced cortical power changes in the LFB predominately in the frontal lobe. Patient 3 did not show sites detectable with ECS.*

to be more sensitive in identifying the Wernicke area (100%) than the Broca area (72.2%). The cumulative findings demonstrate the HFB is uniquely suited to identifying the Wernicke area, whereas a combination of the HFB and LFB is important for optimizing Broca localization. Additionally, the use of multiple sensory cues (ie, visual and auditory) further enhances sensitivity in identifying functional sites.

Substantial attention has been given to understanding how electrical signals, such as EEG and ECoG, correlate to cognitive functions. These experimental approaches have led to our current understanding of how cortical oscillations change when cortex becomes active and engaged in a task. There are several named frequency bands that show consistent changes. Commonly, these

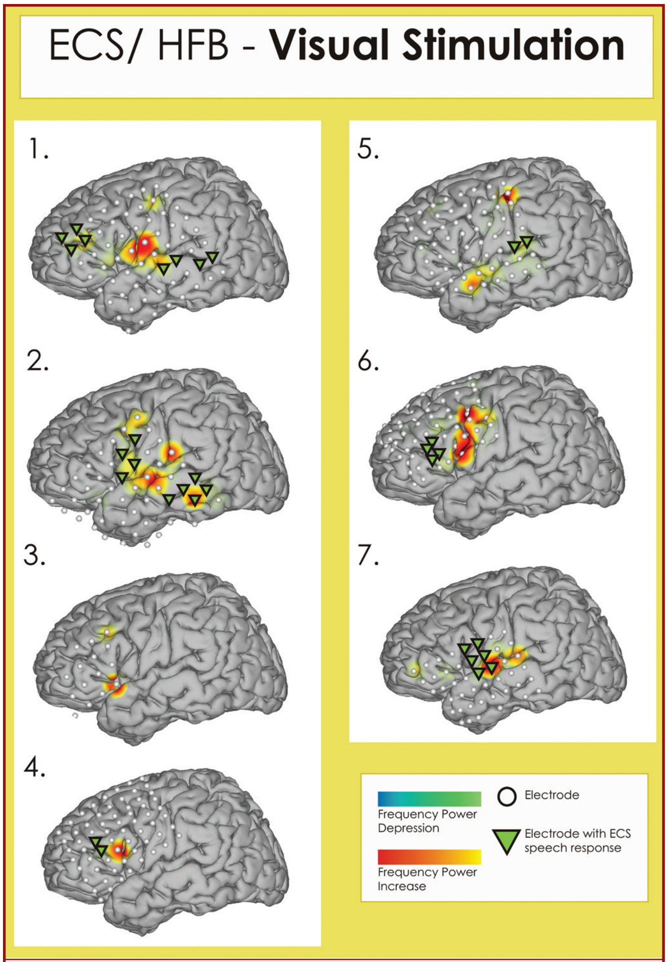

FIGURE 4. *Comparison of stimulation mapping and high-frequency band (HFB) power alteration for visual cued speech task. The figure shows, for patients 1 to 7, the grid electrodes and the regions of cortex identified on the template brain which demonstrate significant HFB power alteration in context to the electrodes that induced speech error/arrest with electrocortical stimulation (ECS). Patient 3 did not show sites detectable with ECS.*

have been described in context of sensorimotor cortical activation. The notable frequencies comprise mu (8-12 Hz), beta (18-26 Hz), and gamma (> 30 Hz) oscillation.[11-13] As mentioned earlier, the lower frequencies of mu and beta are thought to be produced by thalamocortical circuits, which decrease in amplitude in association with actual or imagined movements.[12,13] In general, these lower-frequency bands tend to have a wider cortical distribution. Higher frequencies (> 30 Hz), or gamma rhythms, are thought to be produced by smaller cortical circuits.[26] These frequencies increase in amplitude with cortical activation and tend to have a more cortically focal anatomical distribution for signal change. On a functional level, several studies have revealed that higher frequencies carry highly specific information about cortical processing in regard to speech, motor movements, and motor intention.[9-11,14-16]

In the context of language processing, these high- and low-frequency phenomena show distinct changes with regard to Wernicke and Broca regions. This differential cortical activation, as evidenced by the variable sensitivity and specificity of HFB and LFB in identifying Broca and Wernicke sites, supports the concept that separable cortical networks are participating in receptive and expressive speech and thus require separate consideration for mapping. The LFB and HFB were differentially useful for the identification of expressive and receptive language cortex. The HFB was much more sensitive (100%) than the LFB in identifying the Wernicke area (38.5%). The HFB, however, was less sensitive than the LFB in identifying the Broca area (50% and 55.6%, respectively), and it is only when combined that a higher sensitivity is achieved (77.2%). This finding may be explained by the different origins postulated for LFB and HFB activity. The LFB, which encompasses the mu and beta frequency bands, has been closely associated with processing of motor movements and motor imagery.[12,13] As mentioned earlier, these rhythms are thought to represent thalamocortical circuits, which have broad cortical projections. Given that the Broca region is associated with the expression of speech and its motor articulation, the low-frequency sensitivity may represent the increased motor component in processing speech. The HFB encompasses what are classically known as gamma rhythms. These higher-frequency rhythms have been shown to be more closely associated with smaller neuronal ensembles in cortex.[11,26] Because the reception of speech primarily involves the cortical integration of visual, acoustic, phonologic, and semantic information, this may explain the more prominent role of higher frequencies associated with the identification of the Wernicke areas relative to the Broca area.[10,27] Thus, the high sensitivity and specificity of the HFB for the Wernicke area and the finding that LFB has a better sensitivity and specificity than the HFB in identifying the Broca area suggest that both frequency bands are necessary for ECoG mapping of language areas.

Our finding that ECoG mapping of language sites is highly sensitive and less specific is distinct from previous findings by Sinai et al[8] The similarities and differences in the mapping methodology underline some key elements to using active cortical signals for functional localization. Sinai et al[17] reported low sensitivity but high specificity (38% and 78%, respectively) in their study of mapping during a picture-naming task. These experimenters included only high-frequency gamma oscillations in their analysis, and their experimental task, picture naming, differed from both our auditory and visual (word repetition) tasks. In our study, results were similar when sensitivity and specificity for a visual stimulus using high frequencies were analyzed in isolation (51.6% and 77.5%, respectively). Our results differed when visual and auditory stimulus cues were combined. Sensitivity for identifying a speech site increased substantially to 71%. When low frequencies were also incorporated, the sensitivity was further increased to 83.9%. The specificity, however, was decreased with the inclusion of auditory stimuli and the LFB, to 59.9% and 40.4%, respectively. A qualitative inspection of the brain activation maps revealed that auditory and visual modalities activated different areas of the brain. This suggests that there are multiple neural networks involved in receptive and expressive language, each of which may be activated under different circumstances. This underscores the fact different cortical networks are likely participating in language processing and require multiple language modalities to optimally identify and preserve them.

A comparison of our results with those of a different study, an investigation of the use of EFAM for motor mapping (using the same methods), highlights the differences in cortical processing of language and motor tasks.[9] Electrocorticographic frequency alteration mapping for motor mapping was reported to have a sensitivity of 100% for both tongue and hand movements, a specificity of 79% for tongue movements, and a specificity of 74% for hand movements. The sensitivity and specificity for EFAM was somewhat reduced when speech tasks were compared against motor tasks (sensitivity 100% versus 83.9%, and specificity of 74% versus 40.4%). The greater sensitivity and specificity of EFAM for identifying motor over language sites may be explained by the different cortical and cognitive organizations associated with the 2 functions. The execution of a motor movement is fundamentally associated with primary motor cortex, which is locally organized in a columnar fashion (< 1 mm) and more broadly organized on a somatopic level with various regions of the body (ie, the homunculus). Activations in this region induced by motor activations are likely to have a relatively focal and more robust change in cortical activity. Speech processing, however, involves a broader network of cortex (ie, inferior frontal lobe and posterior temporal lobe) with multiple levels of sensory and cognitive integration (ie, acoustic, visual, phonologic, lexical, and semantic).[27] Thus, because of the multimodal nature of speech and the distributed cortical networks involved in language, EFAM mapping is likely to capture nonessential sites associated with, but not essential to, the language pathway. This is supported by our finding that an EFAM analysis combining the auditory and visual modalities increased sensitivity and reduced specificity. The 2 modalities activated different neural networks, enhancing detection of critical sites, but reduced specificity because of more associated networks being concomitantly activated. Despite their differences, both the motor EFAM study and our language study emphasize the importance of patients performing multiple tasks to maximize the utility of EFAM mapping. In the case of motor mapping, patients should be asked to move more than 1 body part, such as the tongue and hand, and in the case of language mapping, patients should be presented with stimuli of different modalities—auditory and visual—for optimal localization with this technique.

The results of our study suggest that EFAM could be used as an adjunct to ECS for mapping of language cortex in neurologic surgery. The high sensitivity of EFAM for language sites suggests that EFAM-positive sites could be used to identify high-probability starting points for language mapping. The high sensitivity and specificity of HFB in identifying the Wernicke area indicates that sites of HFB cortical activation should be given highest priority. Additionally, EFAM mapping may be helpful in situations where ECS mapping is unhelpful or impossible, when ECS results are negative or cannot be attained due to afterdischarges or pain on stimulation. It is important to note, however, that postoperative morbidity was not assessed in this series. Understanding how these EFAM changes relate to surgical resection will require further study in a larger number of patients where postsurgical outcomes have been assessed and defined relative to resection of EFAM-identified tissue.

Although this study points to many potential uses for EFAM mapping of language cortex, there are certain limitations to the method described. The purpose of this article was not to alter the treatment of invasively monitored human subjects. The work proposes a technique that could potentially be a useful tool to the neurosurgeon or neurologist in identifying a functional cortical site that is associated with speech. In the same light that somatosensory evoked potentials provide supporting or clarifying information where sensorimotor cortex may be for further interrogation with stimulation, we show evidence that this technique could provide some clarifying information for the assessment of speech. This is indeed a preliminary study intended to demonstrate proof of principle that passive techniques for speech-localizing aides are possible. Because the method requires, at most, half the time to perform as cortical stimulation (24-48 minutes versus usually 2 hours for stimulation of entire grid array), interrogates the entire grid at once (versus serial site interrogation with stimulation), and does not pose any additional risk of afterdischarges, there is indeed some potential for utility. Although sufficient for a proof of principle in the technique, further research must be conducted in a larger population of patients with epilepsy to determine whether this method will alter clinical and functional outcomes. Also of note, because cortical mapping is critical in patients with tumors or arteriovenous malformations, investigations into the use of EFAM mapping in patients with grossly abnormal cortical tissue will be important. Further investigation in a larger patient population will be required to more definitively assess how these lesions may affect the ECoG signal associated with language functions.

From a scientific standpoint, there are also some notable caveats. Cortical activations across the HFB and LFB tended to be centered over the inferior and posterior frontal lobe and posterior superior temporal lobe. The substantial involvement of primary motor cortical areas support motor theories of speech processing.[28-30] Activations in other areas posited to be involved in processing speech, such as the anterior temporal lobe and parietal regions, were less prominent.[27] The EFAM method, however, took the time of both cue perception and word articulation in a single time block. This broad average may reduce the sensitivity to detecting more subtle changes associated with the cognitive task of speech processing and articulation. Further refinement of this method (both from a mapping perspective and a neuroscientific method) may include separating these different components of perception and articulation.

In conclusion, our results indicate that EFAM is a safe and potentially useful adjunct to ECS in mapping language cortex for neurologic surgery. Electrocorticographic frequency alteration mapping may improve the efficiency of cortical mapping with ECS, as well as provide an alternative method of mapping language cortex when ECS is not a viable option. Further studies will be required to define whether this technique will alter functional outcomes in the future.

Disclosure

Grant support for this work was received from the James S. McDonnell Higher Brain Function Grant, the Department of Defense, the National Institute of Health, and the Children's Discovery Institute.

REFERENCES

1. Berger MS, Kincaid J, Ojemann GA, Lettich E. Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. *Neurosurgery*. 1989;25(5):786-792.
2. Burchiel KJ, Clarke H, Ojemann GA, Dacey RG, Winn HR. Use of stimulation mapping and corticography in the excision of arteriovenous malformations in sensorimotor and language-related neocortex. *Neurosurgery*. 1989;24(3):322-327.
3. Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS. Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. *J Neurosurg*. 2004;100(3):369-375.
4. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg*. 1989;71(3):316-326.
5. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18-27.
6. Blume WT, Jones DC, Pathak P. Properties of after-discharges from cortical electrical stimulation in focal epilepsies. *Clin Neurophysiol*. 2004;115(4):982-989.
7. Lesser RP, Luders H, Klem G, Dinner DS, Morris HH, 3rd, Hahn J. Ipsilateral trigeminal sensory responses to cortical stimulation by subdural electrodes. *Neurology*. 1985;35(12):1760-1763.
8. Sinai A, Bowers CW, Crainiceanu CM,et al. Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. *Brain*. 2005;128(pt 7):1556-1570.
9. Leuthardt EC, Miller K, Anderson NR, et al. Electrocorticographic frequency alteration mapping: a clinical technique for mapping the motor cortex. *Neurosurgery*. 2007;60(4 suppl 2):260-270; discussion 270-261.
10. Crone NE, Boatman D, Gordon B, Hao L. Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001. *Clin Neurophysiol*. 2001;112(4):565-582.
11. Crone NE, Miglioretti DL, Gordon B, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain*. 1998;121(Pt 12):2301-2315.
12. McFarland DJ, Miner LA, Vaughan TM, Wolpaw JR. Mu and beta rhythm topographies during motor imagery and actual movements. *Brain Topogr*. 2000;12(3):177-186.
13. Pfurtscheller G, Graimann B, Huggins JE, Levine SP, Schuh LA. Spatiotemporal patterns of beta desynchronization and gamma synchronization in corticographic data during self-paced movement. *Clin Neurophysiol*. 2003;114(7):1226-1236.
14. Brown EC, Rothermel R, Nishida M, et al. In vivo animation of auditory-language-induced gamma-oscillations in children with intractable focal epilepsy. *Neuroimage*. 2008;41(3):1120-1131.
15. Crone NE, Hao L, Hart J, Jr, et al. Electrocorticographic gamma activity during word production in spoken and sign language. *Neurology*. 2001;57(11):2045-2053.
16. Tanji K, Suzuki K, Delorme A, Shamoto H, Nakasato N. High-frequency gamma-band activity in the basal temporal cortex during picture-naming and lexical-decision tasks. *J Neurosci*. 2005;25(13):3287-3293.
17. von der Malsburg C. Binding in models of perception and brain function. *Curr Opin Neurobiol*. 1995;5(4):520-526.
18. Korzeniewska A, Kus R, Franaszczuk P, Crainiceanu C, Crone NE. Dynamic high-gamma interactions during language-related task performance. *Epilepsia*. 2005;46:317.
19. Sinai A, Franaszczuk PJ, Crone NE. Electrocorticographic spectral responses during auditory vs. visual lexcial semantic processing. *Epilepsia*. 2005;46(suppl 8):71-72.

20. Schalk G, McFarland DJ, Hinterberger T, Birbaumer N, Wolpaw JR. BCI2000: a general-purpose brain-computer interface (BCI) system. *IEEE Trans Biomed Eng*. 2004;51(6):1034-1043.
21. Marple SL. *Digital spectral analysis with applications.* Englewood Cliffs, NJ: Prentice-Hall; 1987.
22. Fox PT, Perlmutter JS, Raichle ME. A stereotactic method of anatomical localization for positron emission tomography. *J Comput Assist Tomogr*. 1985;9(1):141-153.
23. Talairach J, Tournoux P. *Co-Planar Sterotaxic Atlas of the Human Brain.* New York: Thieme Medical Publishers, Inc., 1988.
24. http://ric.uthscsa.edu/projects/talairachdaemon.html. Accessed 2007
25. http://afni.nimh.nih.gov/afni/suma. Accessed 2007
26. Heldman DA, Wang W, Chan SS, Moran DW. Local field potential spectral tuning in motor cortex during reaching. *IEEE Trans Neural Syst Rehabil Eng.* 2006;14(2): 180-183.
27. Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*. 2007;8(5):393-402.
28. Fadiga L, Craighero L, Buccino G, Rizzolatti G. Speech listening specifically modulates the excitability of tongue muscles: a TMS study. *Eur J Neurosci*. 2002;15(2):399-402.
29. Gow DW, Jr., Segawa JA. Articulatory mediation of speech perception: a causal analysis of multi-modal imaging data. *Cognition*. 2009;110(2):222-236.
30. Liberman AM, Mattingly IG. The motor theory of speech perception revised. *Cognition*. 1985;21(1):1-36.