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# In-Vivo Animation of Auditory-Language-Induced Gamma-Oscillations in Children with Intractable Focal Epilepsy

**Erik C. Brown**[1], **Robert Rothermel**[4], **Masaaki Nishida**[2], **Csaba Juhász**[2,3], **Otto Muzik**[2,5], **Karsten Hoechstetter**[7], **Sandeep Sood**[6], **Harry T. Chugani**[2,3,5], and **Eishi Asano**[2,3,*]

1*MD/PhD Program, School of Medicine, Wayne State University, Detroit, Michigan, 48201, USA*

2*Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, 48201, USA*

3*Department of Neurology, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, 48201, USA*

4*Department of Psychiatry, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, 48201, USA*

5*Department of Radiology, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, 48201, USA*

6*Department of Neurosurgery, Children's Hospital of Michigan, Wayne State University, Detroit, Michigan, 48201, USA*

7*MEGIS Software GmbH, Munich, Germany*

## Abstract

We determined if high-frequency gamma-oscillations (50- to 150-Hz) were induced by simple auditory communication over the language network areas in children with focal epilepsy. Four children (ages: 7, 9, 10 and 16 years) with intractable left-hemispheric focal epilepsy underwent extraoperative electrocorticography (ECoG) as well as language mapping using neurostimulation and auditory-language-induced gamma-oscillations on ECoG. The audible communication was recorded concurrently and integrated with ECoG recording to allow for accurate time-lock upon ECoG analysis. In three children, who successfully completed the auditory-language task, high-frequency gamma-augmentation sequentially involved: i) the posterior superior temporal gyrus when listening to the question, ii) the posterior lateral temporal region and the posterior frontal region in the time interval between question completion and the patient's vocalization, and iii) the pre- and post-central gyri immediately preceding and during the patient's vocalization. The youngest child, with attention deficits, failed to cooperate during the auditory-language task, and high-frequency gamma-augmentation was noted only in the posterior superior temporal gyrus when audible questions were given. The size of language areas suggested by statistically-significant high-frequency gamma-augmentation was larger than that defined by neurostimulation. The present method can provide in-vivo imaging of electrophysiological activities over the language network areas during language processes. Further studies are warranted to determine whether recording of language-induced gamma-oscillations can supplement language mapping using neurostimulation in presurgical evaluation of children with focal epilepsy.

*Corresponding Author: Eishi Asano, MD, PhD, MS (CRDSA), Address: Division of Pediatric Neurology, Children's Hospital of Michigan. 3901 Beaubien St., Detroit, MI, 48201, USA. Phone: 313-745-5547; FAX: 313-745-0955; E-mail: eishi@pet.wayne.edu.

### Keywords

quantitative subdural electroencephalography (EEG) recording; pediatric epilepsy surgery; electrical brain stimulation; event-related potentials; tuberous sclerosis complex

## INTRODUCTION

Cortical areas essential for language are highly variable in location between individuals with focal epilepsy (Ojemann et al., 1989; Duchowny et al., 1996). Thus, functional cortical mapping for language is often performed in patients with intractable neocortical epilepsy to assess the risk of language deficit following resection of the presumed epileptogenic zone. Neurostimulation via implanted subdural electrodes has been demonstrated as a powerful technique for language mapping in a large number of patients and remains today's 'gold-standard' for such use. However, a recent study found neurostimulation inadequate for language mapping in children under age 10 years (Schevon et al., 2007), and alternative language mapping techniques would be highly desirable in these cases.

Quantitative measurement of high-frequency gamma-range oscillations (80- to 100-Hz) on extraoperative electrocorticography (ECoG) during a picture naming task has been proposed as an alternative language mapping technique. Utilizing picture naming tasks, spatial concordance was observed between the language areas determined by such ECoG analysis and neurostimulation in presurgical evaluation for patients ranging in age from mid-adolescence well into adulthood (Crone et al., 2001b; Sinai et al., 2005). However, the literature does not reveal such language mapping by ECoG analysis performed upon patients younger than mid-adolescence.

In the present study, we determined *'where'* and *'when'* an auditory communication task increased high-frequency gamma-oscillations (50- to 150-Hz) on subdural electrodes implanted on the left hemisphere in children with intractable focal epilepsy. We also determined the spatial relationship between the presumed language areas suggested by increased high-frequency gamma-oscillations and those suggested by neurostimulation as well as the brain's anatomical structures.

## MATERIALS AND METHODS

### Subjects

The present study included four native English speaking children who were diagnosed to have intractable focal epilepsy with the presumed epileptogenic zone in the left hemisphere (3 girls ages 7, 9 and 10 years; 1 boy age 15 years). All patients underwent a two-stage epilepsy surgery between January and May of 2007. All four children underwent preoperative scalp video-electroencephalography (video-EEG), preoperative magnetic resonance imaging (MRI), 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography (FDG PET), preoperative neuropsychological examination, extraoperative intracranial electrocorticography (ECoG), and extraoperative functional cortical mapping for language using neurostimulation. Recording of high-frequency gamma-oscillations was employed on ECoG, while each patient was evaluated for baseline language performance. The study was approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the parents or guardians of all subjects.

Clinical data are summarized in Table 1. **Patient 1** had previously undergone unsuccessful tumor resection of the superior portion of the left precentral gyrus at another institution. **Patient 2** possessed a solitary tumor in the left superior frontal region. **Patient 3** had multiple cortical

tubers involving both hemispheres. MRI was normal in **patient 4** but FDG PET scan showed widespread cortical regions with glucose hypometabolism in the left hemisphere.

**Patient 3** underwent preoperative intracarotid sodium amobarbital procedure (also known as Wada test) as part of her neuropsychological evaluation; left-hemispheric language dominance was proven. Language dominance was assumed to be left-hemispheric in **patient 1** and **patient 2** due to right-handedness (Knecht et al., 2000). The assumption of left-hemispheric language dominance in **patient 2** was also supported by the prolonged post-ictal aphasia that characterized her seizures. Due to left-handedness and widespread glucose hypometabolism involving the left hemisphere, **patient 4** had less certain lateralization of language dominance prior to resective surgery.

### Subdural electrode placement

For extraoperative video-ECoG recording, platinum grid electrodes (10mm inter-contact distance; 4mm diameter; Ad-tech, Racine, WI, USA) were surgically implanted on the presumed epileptogenic hemisphere. In all patients, electrodes also covered the lower pre- and post-central gyri, posterior inferior frontal region, and lateral temporal region. Additionally, electrode strips were placed in the inter-hemispheric space to record the ECoG of medial frontal, parietal or occipital regions. One or more additional strips were also placed under the medial temporal region. The total number of electrode contacts ranged from 74 to 128 (Table 1).

### Coregistration of subdural electrodes on individual three-dimensional MRI

MRI including a T1-weighted spoiled gradient echo image as well as fluid-attenuated inversion recovery image was obtained preoperatively. Planar x-ray images (lateral and anteroposterior) were acquired with the subdural electrodes in place for electrode localization on the brain surface; three metallic fiducial markers were placed at anatomically well-defined locations on the patient's head for co-registration of the x-ray image with the MRI. A three-dimensional surface image was created with the location of electrodes as directly defined on the brain surface, as previously described (von Stockhausen et al., 1997; Muzik et al., 2007).

### Extraoperative video-ECoG recording

Extraoperative video-ECoG recordings were obtained for three to five days, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA), which has an input impedance of 200 MΩ, a common mode rejection ratio greater than 110 dB, an A/D conversion of 16 bits, a sampling frequency at 1,000-Hz and the amplifier band pass at 0.08- to 300-Hz. ECoG signals were re-montaged to an average reference, to obtain reference-free topographic maps of spectral measures. Channels contaminated with large interictal epileptiform discharges or artifacts were excluded from the average reference. Antiepileptic medications were discontinued or reduced during ECoG monitoring until a sufficient number of habitual seizures were captured, and seizure onset zones were visually identified.

### Language mapping using time-frequency analysis of EcoG

**Auditory language task—**All tests necessary for language mapping by measurement of auditory-language-induced gamma-oscillations were performed while each patient was awake and comfortably seated on the bed. The patient received a series of 60 custom-made question-and-answer trials, and the patient's baseline performance was evaluated. Provided questions ranged from 1 to 2 seconds in duration. All questions were read aloud by a neuropsychologist (R.R.) and designed to elicit 1 or 2 word answers with nouns; i.e. Q: 'What flies in the sky?' The list of questions used in the present study is available in Table S1. This audible session

was recorded using a Digital Voice Recorder (WS-300M, Olympus America Inc, Hauppauge, NY, USA) concurrently with ECoG recording, and the amplified audio waveform was integrated into the Digital ECoG Recording System (Figure S1). Subsequently, the onset of auditory question as well as the onset of the patient's vocalization of the answer was marked for each question-and-answer session (Figure 1). Cool Edit Pro version 2.00 (Syntrillium Software Corp., Phoenix, AZ, USA) was used to visually and audibly aid in the manual determination of the onset of the patient's vocalization (Figure 1).

**Analysis of high-frequency gamma-oscillations relative to 'the onset of patient's vocalization'—**Data analysis was performed using BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany). Language event-related amplitude modulations were evaluated using the trigger point set at the onset of patient's vocalization. Especially, alteration of high-frequency gamma-range (at 50-Hz or above) amplitude (unit: μV) time-locked to patient's vocalization was assessed; this analytic method was designed to evaluate sequential brain activation associated with comprehension, word retrieval and vocalization (Figure 2).

The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: i) patient's vocalization of the answer must be not longer than 1,000-msec in duration; ii) the variability of delay between offset of the question and onset of the patient's vocalization must be within 1,000-msec across trials; iii) a period of silence (as a reference period) lasting 200-msec must be available between 1,000- to 1,400-msec after onset of the patient's vocalization; iv) another period of silence lasting 200-msec must be present immediately prior to the above-defined reference period of 200-msec, in order to minimize the potential effect of lingering self-vocalization-induced amplitude modulation on each reference period; and v) the patient only vocalized a correct answer. The exclusion criteria included: i) ECoG trace was affected by movement artifacts; ii) ECoG trace was affected by electrographic seizures; and iii) ECoG trace from the left superior temporal gyrus was affected by runs of interictal epileptiform discharges. All ECoG epochs (starting 2,000-msec prior to and ending 1,400-msec after the trigger) which satisfied all of the inclusion and exclusion criteria were utilized for the time-frequency ECoG analysis described below.

Each suitable ECoG trial was transformed into the time-frequency domain using complex demodulation technique as featured in the BESA software (Hoechstetter et al., 2004; Fan et al., 2007). In that technique, the time-frequency transform was obtained by multiplication of the time-domain signal with a complex exponential, followed by a low pass finite impulse response (FIR) filter of Gaussian shape. Details on the complex demodulation technique for time-frequency transformation are described elsewhere (Papp and Ktonas, 1977; Hoechstetter et al., 2004). This is equivalent to a wavelet transformation with constant wavelet width across frequencies. As a result of this transformation, the signal was assigned a specific amplitude and phase as a function of frequency and time (relative to the onset of the patient's vocalization). In this study, only the amplitude averaged across all trials, was used for further analysis. Time-frequency transformation was performed for frequencies between 30- and 200-Hz and latencies between -2,000 msec and +1,400 msec relative to the onset of the patient's vocalization, in steps of 5-Hz and 10 msec. This corresponded to a time-frequency resolution of +/-7.1 Hz and +/-15.8 msec (50% power drop of the FIR filter).

At each time-frequency bin we analyzed the percentage change in amplitude (averaged across trials) relative to the mean amplitude in a reference period, defined as the resting state following patient's vocalization. This parameter is commonly termed "event-related synchronization and desynchronization" (Pfurtscheller et al., 1979), whereas a less suggestive terminology is "temporal spectral evolution" (TSE) (Salmelin and Hari, 1997).

To test for statistical significance for each obtained TSE value, two-step statistics was performed using the BESA software: First, statistics based on bootstrapping approach (Davidson et al., 1999) was applied to obtain an uncorrected p-value at each time-frequency bin. In a second step, correction for multiple testing was performed (each electrode was analyzed at 11,935 time-frequency bins, with TSE values at neighboring bins being partially dependent). A modification of the correction developed by Simes (1986) was used as suggested for time-frequency analysis by Auranen (2002): p values of one frequency bin and channel were sorted in ascending order ($p_i$, i=1,…,N). The maximum index m in the sorted array for which $p_i < \alpha*i/N$ was determined. All uncorrected p-values with i<m were accepted as significant. The corrected significance level α was set to 0.05. This approach is less conservative than the classic Bonferroni correction and is specifically suited for partially dependent multiple testing (Simes, 1986; Auranen, 2002). In all figures, blue color indicated a significant decrease of amplitude, red color a significant increase in the corresponding time-frequency bin relative to the baseline as obtained by this procedure.

An additional correction for testing in multiple electrodes (the number of subdural electrodes ranged from 74 to 128 across subjects) was employed; TSE values in a given electrode were declared to be statistically significant only if a minimum of 8 voxels in the high-frequency gamma-band range were arranged in a continuous array spanning (i) at least 20-Hz in width and (ii) at least 20-msec in duration. Such correction provides a very small probability of Type-I error in determination of cortical activation or deactivation. We recognize that this analysis may potentially underestimate gamma-modulations with a restricted frequency band (less than 20-Hz in width) or that with a short duration (less than 20-msec in duration).

**Analysis of high-frequency gamma-oscillations relative to 'the onset of auditory question'—**Language event-related amplitude modulations were also evaluated using the trigger point set at the onset of auditory question, and this analytic method was designed to evaluate brain activation associated with the initiation of auditory question. Limitation of this analytic method includes a potential temporal overlap between the sounds presented by the neuropsychologist and the sounds produced by the patient. Since the duration of questions was not uniform, the onset of patient's vocalization in a session with short question may begin before the offset of auditory question in another session with a relatively longer question (Figure 2).

The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: i) at least 300-msec of silence occurred before the onset of auditory question; and ii) the patient was observed to have heard the question - indicated by any relevant response. The same exclusion criteria described above were applied. All 3,300-msec ECoG epochs (starting 300-msec prior to and ending 3,000-msec after the onset of auditory question) which satisfied all of the inclusion and the exclusion criteria were utilized for the time-frequency ECoG analysis. A reference period of 200-msec was set within the period of silence at 300- to 100-msec prior to the auditory question. Alteration of ECoG amplitude was determined using the statistical approach as described above.

## Language mapping using neurostimulation

Language mapping by neurostimulation was performed during extraoperative ECoG recording, using a method similar to those described previously (Sinai et al., 2005; Haseeb et al., 2007). Questions that could not be answered quickly and reliably at the baseline evaluation were eliminated from the protocol used in stimulation mapping. A pulse-train of electrical stimuli was delivered using the Grass S88 constant-current stimulator (Astro-Med, Inc, West Warwick, RI, USA). To minimize stimulation-induced seizure risk, a loading dose of phenytoin was administered intravenously prior to the mapping session (Haseeb et al, 2007). To determine

the presence of after-discharges, subdural ECoG and video were recorded continuously during the procedure.

Subdural electrode pairs were stimulated by an electrical pulse-train of 10-sec maximum duration using pulses of 300-μsec duration. Initially, stimulus intensity was set to 3-mA and stimulus frequency was set to 50-Hz. Stimulus intensity was increased from 3- to 9-mA in a stepwise manner by 3-mA until a clinical response or after-discharge was observed. During each period of 10-sec stimulation, each patient was asked to answer two brief questions used in the above-mentioned language mapping task. Other tasks such as picture naming, counting and reciting ABC's were also assigned as needed. When the patient failed to answer a question or complete the assigned task during a stimulation period, he/she was asked why he/she failed. Brain regions at which stimulation consistently induced a clinical response were declared eloquent for that function. When after-discharge without an observed clinical response or when neither clinical response nor after-discharge was induced by the maximally-intense stimuli, the brain region was declared to have not been proven eloquent. This neurostimulation session required 1 to 2 hours of patient time.

### Delineation of ECoG data on three-dimensional MRI

ECoG data for each electrode channel were exported to the given electrode site on the individual three-dimensional brain surface in two different ways. In order to delineate *'when'*, *'where'* and *'at what frequency band'* significant alteration of ECoG amplitude occurred, time-frequency plot matrixes created above were placed onto a three-dimensional MRI at the cortical sites corresponding to their respective subdural electrode positions (Figures 2, 3, S2 - S5). In order to animate *'when'*, *'where'* and *'how many fold'* high-frequency gamma-oscillations were increased, 'gamma-range amplitude' (defined as the amplitude averaged across 50- to 150-Hz frequency bands and normalized to that of the baseline) was sequentially delineated on the individual three-dimensional MRI (Figure 2), using a method similar to that previously described (Asano et al., 2005). In short, 'gamma-range amplitude' for each electrode channel at each 10-msec epoch was registered into the SurGe Interpolation Software 1.2 (Web site: http://mujweb.cz/www/SurGe/surgemain.htm), and interpolated topography map of 'gamma-range amplitude' at each 10-msec epoch was accurately superimposed to the individual three-dimensional MRI. Finally, all interpolated topography maps were sequentially registered to the Microsoft Windows Movie Maker 5.1 (Microsoft Corporation, Redmond, WA, USA), and this procedure yielded a movie file showing a sequential alteration of high-frequency gamma-oscillations related to language activity (Video S1).

## RESULTS

### High-frequency gamma-oscillations time-locked to patient's vocalization

Behavioral data are presented in Table 2. Three (**patients 1 - 3**) out of four patients satisfactorily completed the auditory-language task. A total of 42, 44, and 40 trials, respectively, were considered to be suitable and included for time-frequency analysis time-locked to the onset of patient's vocalization. About one-third of epochs failed to be included, mostly because vocalization of the answer lasted longer than 1 second, the response was much delayed compared to the others, the answer was not correct, and the presumed reference period of silence was affected by some forms of noise. Conversely, the youngest child with attention deficits (**patient 4**) was highly uncooperative during the question-and-answer session, and only six ECoG epochs were found to be suitable for the analysis. We recognized that **patient 4** more readily answered questions relating to sleep and animals, whereas questions concerning airplanes, hospitals, or everyday objects were of little interest and were often not answered. This question-and-answer session required 10 to 20 minutes of patient time. Data analysis

required up to 4 hours of unmanned computing time. Once the statistical data were processed, a quick review revealed regions of important language function.

Spatial and temporal patterns of amplitude modulations are described in Figures 2, 3, S2 - S5, Table 3 and Video S1 in detail; a substantial inter-subject variability in the spatial distribution of language-induced gamma augmentation was noted. In short, cortical activation mostly presented as increased high-frequency gamma-oscillations at 50- to 150-Hz and sequentially involved: i) the posterior superior temporal gyrus when listening to the question, ii) the posterior inferior-and-middle temporal gyri, the inferior frontal gyrus, the medial-superior frontal region and the medial temporal lobe structure in the time interval between question completion and the patient's vocalization, iii) the pre-and post-central gyri immediately preceding and during the patient's vocalization and iv) the posterior superior temporal gyrus following the patient's vocalization. No significant cortical activation was noted in **patient 4**, probably due to the lack of sufficient number of trials included into the analysis.

### High-frequency gamma-oscillations time-locked to auditory questions

Time-frequency ECoG analysis time-locked to the onset of auditory question was satisfactorily performed for all four patients, and a total of 51, 38, 56, and 28 trials, respectively, were considered to be suitable and included for the analysis. The remaining trials were excluded from the analysis due to the same reasons described above. Although **patient 4** frequently failed to provide correct answers, this child appeared to listen to many questions.

Spatial and temporal patterns of amplitude modulations are described in Figures 2, 3, S2 - S5 and Table 3 in detail. In short, cortical activation involved the posterior superior temporal gyrus when listening to the question in all patients. Further cortical activation was not noted in **patient 4** since she failed to provide correct answers in most trials. In the remaining three patients, subsequent cortical activation involved the brain regions as described in Table 3.

### Relationship between presumed language areas suggested by ECoG analyses and those by neurostimulation

The spatial relationship between the eloquent cortices suggested by ECoG amplitude analyses and neurostimulation is described in Figures 2, 3, S2 - S5 in detail. In short, the language-related cortices suggested by neurostimulation showed evidence of cortical activation on the above-mentioned ECoG analyses. The size of eloquent cortices suggested by ECoG analyses was larger than that of neurostimulation.

Among six electrode pairs of which neurostimulation revealed underlying language functions (1 pair: auditory response; 1 pair: receptive-language response; and 4 pairs: expressive-language response), five pairs included at least an electrode showing language event-related cortical activation on ECoG analyses. The remaining pair was located between two electrodes both showing cortical activation.

Among 11 electrode pairs of which neurostimulation revealed underlying mouth-throat sensory-motor functions, nine pairs included at least an electrode showing cortical activation on the above-mentioned ECoG analysis. Neither electrode pair of which neurostimulation resulted in teeth tingling showed cortical activation on ECoG analyses. An electrode pair, of which neurostimulation resulted in lip movement, was not be satisfactorily assessed by the ECoG analysis time-locked to patient's vocalization, since **patient 4** failed to cooperate to the language tasks as described above.

The spatial relationship between the presumed language areas and the extent of cortical resection is shown in Figures 2, 3, S2 - S5. None of the children developed apparent language deficits postoperatively. Following resective surgery, **patients 1 - 3** have been seizure-free,

while **patient 4** experienced two complex partial seizures (the mean follow-up: 6 months). As expected preoperatively, **Patient 1** developed a slight worsening of hemiparesis in the right-sided upper extremity and **Patient 4** developed a right-sided hemianopsia.

## DISCUSSION

In the present study of children with uncontrolled focal epilepsy, measurement of event-related high-frequency gamma-oscillations delineated not only *'where'* but also *'how'* the brain cortices participated in language activity with high temporal and spatial resolution. In-vivo animation of event-related gamma-oscillations on an individual three-dimensional MRI surface image is a novel technique which increases our understanding of the cortical pathway and activation pattern related to auditory language activity. Localization of the presumed language-related cortices suggested by the ECoG amplitude analyses was concordant with the generally-accepted functional brain map derived from a number of previous studies using other diagnostic modalities. The size of language-related cortices suggested by the ECoG amplitude analyses was generally larger than that by neurostimulation in the present study.

### Successive cortical activations involving the left temporal neocortices

The ECoG amplitude analyses in the present study revealed successive cortical activations involving two distinct temporal neocortical areas. Cortical activation initially involved the superior temporal gyrus and such cortical activation was present during auditory questions. Cortical activation subsequently involved the posterior part of middle or inferior temporal gyri. The observed pattern of cortical activation is consistent with the results in previous human studies. An intraoperative neurostimulation study in 12 adults with brain tumors showed that stimulation of the posterior inferior temporal region temporally elicited semantic paraphasia (Mandonnet et al., 2007). An auditory evoked potential study of healthy adults using object discrimination tasks revealed that an initial cortical potential involved the posterior part of the left superior temporal gyrus 70-msec after stimulus onset and subsequently involved the lateral aspect of the inferior temporal gyrus 200- to 250-msec after stimulus onset (Murray et al, 2006). A study of adults with focal epilepsy using extraoperative ECoG recording demonstrated that gamma augmentation (80- to 100-Hz) was induced by auditory tones in the left superior temporal gyrus (Crone et al., 2001a). Another study of adults with focal epilepsy using intraoperative ECoG recording also showed that auditory tones induced gamma augmentation in the left superior temporal gyrus and that the frequency band of maximum response could appear anywhere from 70 to 160 Hz (often around 100 Hz) (Edwards et al., 2005). A functional-MRI study in healthy adults showed that auditory semantic words stimuli induced increased blood-oxygen-level dependent (BOLD) signals in the left posterior superior temporal gyrus 4-sec after auditory stimuli and subsequently in the posterior part of the middle-and-inferior temporal gyri 10- to 12-sec after the auditory stimuli (Humphries et al., 2007). Thus, we speculate that initial cortical activation in the superior temporal gyrus seen in the present study represented the auditory processing, whereas the secondary activation in the posterior middle-inferior temporal gyri represented the processing of semantic comprehension. Based on the task given in the present study, however, we are not able to determine whether the initial cortical activation in the superior temporal gyrus was specifically responsible for acoustic perception, linguistic function or both of those. Further studies using a contrasting task may address this issue.

### Successive cortical activations in the left supra-sylvian neocortices

The ECoG amplitude analyses in the present study revealed successive cortical activations involving three supra-sylvian neocortices. Cortical activation involved the inferior frontal gyrus and the medial-superior frontal gyrus; such frontal activation occurred prior to activation in the pre- and post-central gyri and subsided with the onset of vocalization. Immediately prior

to and during vocalization, cortical activation involved the pre- and post-central gyri. The observed pattern of such successive cortical activations is consistent with observations from previous studies described below.

It has been shown that adults with focal lesions in the left inferior frontal gyrus often exhibit impaired semantically appropriate word generation (Thompson-Schill et al., 1998). A study of healthy adults showed that repetitive transcranial magnetic stimulation of the left inferior frontal gyrus temporarily blocked both capacities of speaking aloud and internally (Aziz-Zadeh et al., 2005). Studies in adults with focal epilepsy showed that electrical stimulation of the inferior frontal gyrus induced speech arrest as well as evoked potentials in the orofacial representational area of primary motor cortex (Greenlee et al., 2004; Matsumoto et al., 2005). Studies using functional MRI suggested that syntactic and semantic processing tasks induced increased BOLD signals in the inferior frontal gyrus (Embick et al., 2000; Roskies et al., 2001). Thus, we speculate that cortical activation in the inferior frontal gyrus seen in the present study represented the processing of semantically appropriate word generation.

It has been suggested that the medial superior frontal cortices (including the supplementary motor area, the pre-supplementary motor area, and the cingulate gyrus) play a role in voluntary control over the initiation and suppression of vocal utterance, whereas the pre- and post-central gyri carry out voluntary control over the acoustic structure of vocalizations (Jürgens, 2002). A study in monkeys showed that neurostimulation of the cingulate cortex resulted in vocalization (Jürgens and Pratt, 1979). A study of adults with focal epilepsy showed that neurostimulation of the pre-supplementary motor area induced various forms of clinical responses including vocalization, speech arrest and slowing of speech (Fried et al., 1991). It has been also reported that cerebral infarction or surgical resection involving the left medial superior frontal gyrus resulted in temporary mutism, defined as a state where a patient is conscious but unable to talk (Masdeu et al., 1978; Crutchfield et al., 1994). A study of adults with focal epilepsy showed that movement-related potentials were noted in the medial superior frontal gyrus 300-msec prior to voluntary orofacial movements (Ikeda et al., 1992). Functional MRI studies in healthy adults showed that overt verbal fluency tasks induced increased BOLD signals not only in the left inferior frontal gyrus but also in the medial superior frontal gyrus (Abrahams et al., 2003). Thus, we speculate that cortical activation in the medial superior frontal gyrus seen in the present study represented the preparation of fluent vocalization, and that activation in the pre- and post-central gyri represented the active process of voluntary control over the acoustic structure of vocalizations.

### Relationship between the presumed language areas suggested by increased gamma-oscillations and those suggested by neurostimulation

In the present study, the size of language areas suggested by increase of gamma-oscillations was larger than that by neurostimulation, and this observation is in contrast to the observation in a previous study (Sinai et al., 2005) that the size of language areas suggested by neurostimulation was larger than that by analysis of gamma-oscillations. This discrepancy in the results of two studies may be partly attributed to differences in the study population. The present study included only children with focal epilepsy, whereas the study by Sinai et al (2005) included adults and mid-adolescents. Previous studies of young patients with focal epilepsy demonstrated a positive correlation between the age of patients and the number of sites where neurostimulation produced naming errors in language mapping (Ojemann et al., 2003; Schevon et al., 2007). Difference in methodologies between the present study and the study by Sinai et al (2005) also includes the approach to determine significant increase of gamma-oscillations in each electrode site. Our ECoG analysis included a frequency range from 30- to 200-Hz; significant activations across this spectrum were determined using corrected p-values spanning at least 20-Hz frequency bands and 20-msec in duration. On the other hand,

the study by Sinai et al (2005) evaluated sequential changes of ECoG powers at an 80- to 100-Hz band using 100-msec epochs. Finally, it should be also noted that auditory-naming tasks were given in the present study, whereas picture naming tasks were given in the study by Sinai et al (2005).

## Methodological limitations in the present study

Few investigators have reported language mapping using ECoG amplitude modulations in children with uncontrolled focal epilepsy. Potential methodological limitations of such analysis should be discussed. First, data collection for the purpose of functional cortical mapping for language by ECoG required the performance of many simple language tasks to enable statistical analysis. Ideal patient performance involves maintaining a consistent answer delay following the provided questions as well as a period of silence after each answer. This requires a certain level of verbal intelligence and motivation to cooperate that may be hard to find in very young children; i.e. **patient 4** of the present study, a 7-year-old girl, prevented ECoG analysis time-locked to patient vocalization by exhibiting uncooperative behavior.

Significant cortical activation (or deactivation) was determined using corrected p-values. This indicates that cortical activation (or deactivation) could fail to reach significance due to insufficient number of suitable trials. Thus, a number of question-and-answer sessions enjoyable by young children should be prepared to minimize the risk of such a Type-II error in statistical tests. It should be also noted that cortical activation (or deactivation) could fail to reach significance if temporal variability across events of interest is large. In order to minimize such a temporal variability of events, we analyzed the ECoG data using two distinct time-lock triggers initially set at the onset of patient's vocalization and subsequently set at the onset of auditory questions (Figure 2).

In the ECoG analysis time-locked to patient's vocalization, a silent period of 200-msec between answer and question was utilized as a reference period; each 200-msec reference period had twenty time-frequency sampling points for each frequency band. We recognize that usage of a longer reference period would have further increased the statistical power to determine significant cortical activation as well as deactivation. Yet, presence of various types of external sounds (such as coughing and next auditory questions) prevented a reference period from expanding longer than 200-msec in the present study. We recognize that the selection of reference period could have influenced the results in the present study, particularly if there was a lingering brain activation following the offset of the patient's vocalization (Trautner et al., 2006). In the ECoG analysis time-locked to auditory question, on the other hand, we cannot rule out the possibility that expectancy or readiness-related brain activation may have been present during the reference period of 200 msec.

It should be noted that focal alpha- and beta-attenuation (also known as alpha-and beta-desynchronization) have been previously reported as evidence of focal cortical activation (Pfurtscheller, 1977; Crone et al., 1998; Hirata et al., 2004; Miller et al., 2007). ECoG oscillations slower than 30 Hz were not evaluated in the present study, and language-induced alpha- and beta-attenuation could be the subject of future studies.

One of the major limitations of extraoperative ECoG recordings is sampling error. ECoG analysis was limited to the brain region where subdural electrodes were placed. In the present study, subdural electrodes were placed only in the presumed epileptogenic hemisphere; we were not able to evaluate cortical activation in the other hemisphere. **Patient 4** had very little induced gamma-oscillations in the left superior temporal gyrus and no apparent language deficits following the surgical resection involving the left temporal-occipital-parietal region as well as a part of the middle-inferior frontal gyri; we assume **patient 4** had right-sided language dominance. Yet, we were not able to prove language event-related cortical activation

in the right hemisphere, since subdural electrode placement on the right hemisphere was not indicated in this patient.

Antiepileptic drugs may affect the findings of cortical mapping using neurostimulation as well as measurement of gamma-oscillations on ECoG. In the present study, phenytoin was loaded intravenously prior to the mapping session, to minimize stimulation-induced seizure risk. A previous study of healthy volunteers demonstrated that phenytoin elevated motor thresholds to transcranial magnetic stimulation but had no effect on motor-evoked potential amplitudes, silent period duration, or intracortical excitability (Chen et al., 1997).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

Abrahams S, Goldstein LH, Simmons A, Brammer MJ, Williams SC, Giampietro VP, Andrew CM, Leigh PN. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. Hum Brain Mapp 2003;20:29–40. [PubMed: 12953304]

Asano E, Juhász C, Shah A, Muzik O, Chugani DC, Shah J, Sood S, Chugani HT. Origin and Propagation of Epileptic Spasms Delineated on Electrocorticography. Epilepsia 2005;46:1086–1097. [PubMed: 16026561]

Auranen, T. Master's Thesis. Helsinki University of Technology, Department of Electrical and Communications Engineering; Espoo, Finland: 2002. Nonparametric statistical analysis of time-frequency representations of magnetoencephalographic data.

Aziz-Zadeh L, Cattaneo L, Rochat M, Rizzolatti G. Covert speech arrest induced by rTMS over both motor and nonmotor left hemisphere frontal sites. J Cogn Neurosci 2005;17:928–938. [PubMed: 15969910]

Chen R, Samii A, Canos M, Wassermann EM, Hallett M. Effects of phenytoin on cortical excitability in humans. Neurology 1997;49:881–883. [PubMed: 9305361]

Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser RP. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis I. Alpha and beta event-related desynchronization. Brain 1998;121:2271–2299. [PubMed: 9874480]

Crone NE, Boatman D, Gordon B, Hao L. Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article. Clin Neurophysiol 2001a;112:565–582. [PubMed: 11275528]

Crone NE, Hao L, Hart J, Boatman D, Lesser RP, Irizarry R, Gordon B. Electrocorticographic gamma activity during word production in spoken and sign language. Neurology 2001b;57:2045–2053. [PubMed: 11739824]

Crutchfield JS, Sawaya R, Meyers CA, Moore BD 3. Postoperative mutism in neurosurgery. Report of two cases. J Neurosurg 1994;81:115–121. [PubMed: 8207512]

Davidson, AC.; Hinkley, DV. Bootstrap Methods and their Application, Chapter 4.4.1: Studentized bootstrap method. Cambridge University Press; Cambridge: 1999. p. 161-175.

Duchowny M, Jayakar P, Harvey AS, Resnick T, Alvarez L, Dean P, Levin B. Language cortex representation: effects of developmental versus acquired pathology. Ann Neurol 1996;40:31–38. [PubMed: 8687189]

Edwards E, Soltani M, Deouell LY, Berger MS, Knight RT. High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. J Neurophysiol 2005;94:4269–4280. [PubMed: 16093343]

Embick D, Marantz A, Miyashita Y, O'Neil W, Sakai KL. A syntactic specialization for Broca's area. Proc Natl Acad Sci USA 2000;97:6150–6154. [PubMed: 10811887]

Fan J, Byrne J, Worden MS, Guise KG, McCandliss BD, Fossella J, Posner MI. The relation of brain oscillations to attentional networks. J Neurosci 2007;27:6197–6206. [PubMed: 17553991]

Fried I, Katz A, McCarthy G, Sass KJ, Williamson P, Spencer SS, Spencer DD. Functional Organization of Human Supplementary Motor Cortex Studied by Electrical Stimulation. J Neurosci 1991;11:3656–3666. [PubMed: 1941101]

Greenlee JD, Oya H, Kawasaki H, Volkov IO, Kaufman OP, Kovach C, Howard MA, Brugge JF. A functional connection between inferior frontal gyrus and orofacial motor cortex in human. J Neurophysiol 2004;92:1153–1164. [PubMed: 15056683]

Haseeb A, Asano E, Juhasz C, Shah A, Sood S, Chugani HT. Young patients with focal seizures may have the primary motor area for the hand in the postcentral gyrus. Epilepsy Res 2007;76:131–139. [PubMed: 17723289]

Hirata M, Kato A, Taniguchi M, Saitoh Y, Ninomiya H, Ihara A, Kishima H, Oshino S, Baba T, Yorifuji S, Yoshimine T. Determination of language dominance with synthetic aperture magnetometry: comparison with the Wada test. NeuroImage 2004;23:46–53. [PubMed: 15325351]

Hoechstetter K, Bornfleth H, Weckesser D, Ille N, Berg P, Scherg M. BESA source coherence: A new method to study cortical oscillatory coupling. Brain Topography 2004;16:233–238. [PubMed: 15379219]

Humphries C, Binder JR, Medler DA, Liebenthal E. Time course of semantic processes during sentence comprehension: an fMRI study. NeuroImage 2007;36:924–932. [PubMed: 17500009]

Ikeda A, Lüders HO, Burgess RC, Shibasaki H. Movement-related potentials recorded from supplementary motor area and primary motor area. Role of supplementary motor area in voluntary movements. Brain 1992;115:1017–1043. [PubMed: 1393500]

Jürgens U. Neural pathways underlying vocal control. Neurosci Biobehav Rev 2002;26:235–258. [PubMed: 11856561]

Jürgens U, Pratt R. The cingular vocalization pathway in the squirrel monkey. Exp Brain Res 1979;34:499–510. [PubMed: 105921]

Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Flöel A, Ringelstein EB, Henningsen H. Handedness and hemispheric language dominance in healthy humans. Brain 2000;123:2512–2518. [PubMed: 11099452]

Mandonnet E, Nouet A, Gatignol P, Capelle L, Duffau H. Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. Brain 2007;130:623–629. [PubMed: 17264096]

Masdeu JC, Schoene WC, Funkenstein H. Aphasia following infarction of the left supplementary motor area: a clinicopathologic study. Neurology 1978;28:1220–1223. [PubMed: 569781]

Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, Luders HO. Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain 2004;127:2316–2330. [PubMed: 15269116]

Miller KJ, Leuthardt EC, Schalk G, Rao RP, Anderson NR, Moran DW, Miller JW, Ojemann JG. Spectral changes in cortical surface potentials during motor movement. J Neurosci 2007;27:2424–2432. [PubMed: 17329441]

Murray MM, Camen C, Gonzalez Andino SL, Bovet P, Clarke S. Rapid brain discrimination of sounds of objects. J Neurosci 2006;26:1293–1302. [PubMed: 16436617]

Muzik O, Chugani DC, Zou G, Hua J, Lu Y, Lu S, Asano E, Chugani HT. Multimodality Data Integration in Epilepsy. Int J Biomed Imaging. 200710.1155/2007/13963

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;71:316–326. [PubMed: 2769383]

Ojemann SG, Berger MS, Lettich E, Ojemann GA. Localization of language function in children: results of electrical stimulation mapping. J Neurosurg 2003;98:465–470. [PubMed: 12650415]

Papp N, Ktonas P. Critical evaluation of complex demodulation techniques for the quantification of bioelectrical activity. Biomed Sci Instrum 1977;13:135–145. [PubMed: 871500]

Pfurtscheller G. Graphical display and statistical evaluation of event-related desynchronization (ERD). Electroencephalogr Clin Neurophysiol 1977;43:757–760. [PubMed: 72657]

Roskies AL, Fiez JA, Balota DA, Raichle ME, Petersen SE. Task-dependent modulation of regions in the left inferior frontal cortex during semantic processing. J Cogn Neurosci 2001;13:829–843. [PubMed: 11564326]

Salmelin R, Hari R. Spatiotemporal characteristics of sensorimotor MEG rhythms related to thumb movement. Neuroscience 1994;60:537–550. [PubMed: 8072694]

Schevon CA, Carlson C, Zaroff CM, Weiner HJ, Doyle WK, Miles D, Lajoie J, Kuzniecky R, Pacia S, Vazquez B, Luciano D, Najjar S, Devinsky O. Pediatric Language Mapping: Sensitivity of Neurostimulation and Wada Testing in Epilepsy Surgery. Epilepsia 2007;48:539–545. [PubMed: 17284300]

Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73:751–754.

Sinai A, Bowers CW, Crainiceanu CM, Boatman D, Gordon B, Lesser RP, Lenz FA, Crone NE. Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. Brain 2005;128:1556–1570. [PubMed: 15817517]

Thompson-Schill SL, Swick D, Farah MJ, D'Esposito M, Kan IP, Knight RT. Verb generation in patients with focal frontal lesions: a neuropsychological test of neuroimaging findings. Proc Natl Acad Sci USA 1998;95:15855–15860. [PubMed: 9861060]

Trautner P, Rosburg T, Dietl T, Fell J, Korzyukov OA, Kurthen M, Schaller C, Elger CE, Boutros NN. Sensory gating of auditory evoked and induced gamma band activity in intracranial recordings. Neuroimage 2006;32:790–798. [PubMed: 16809054]

von Stockhausen HM, Thiel A, Herholz K, Pietrzyk U. A convenient method for topographical localization of intracranial electrodes with MRI and a conventional radiograph. NeuroImage 1997;5:S514.Abstract

## Abbreviations

**ECoG**
: electrocorticography

**MRI**
: magnetic resonance imaging

**FDG**
: 2-deoxy-2-[18F]fluoro-D-glucose

**PET**
: positron emission tomography

**BOLD**
: blood-oxygen-level dependent

**EEG**
: electroencephalography

**FIR**
: finite impulse response

**TSE**
: temporal spectral evolution

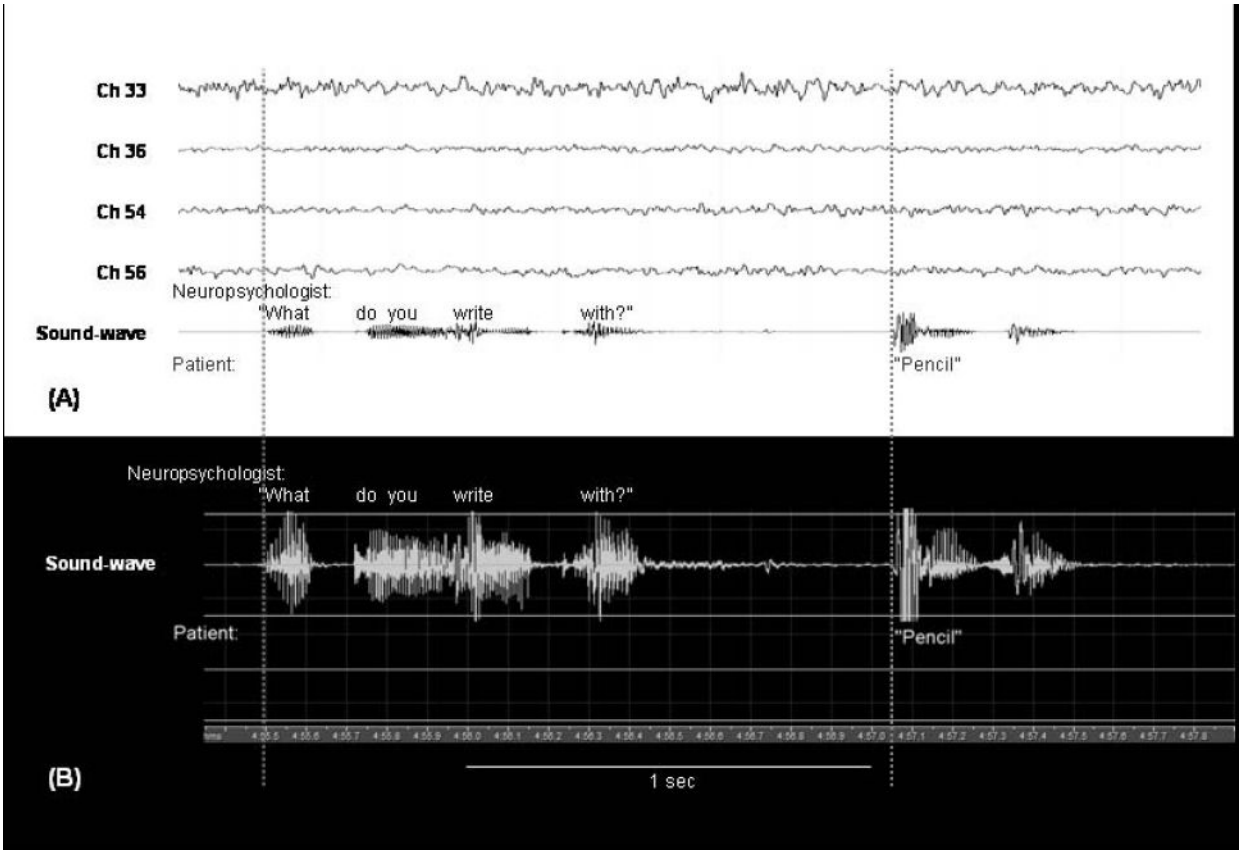
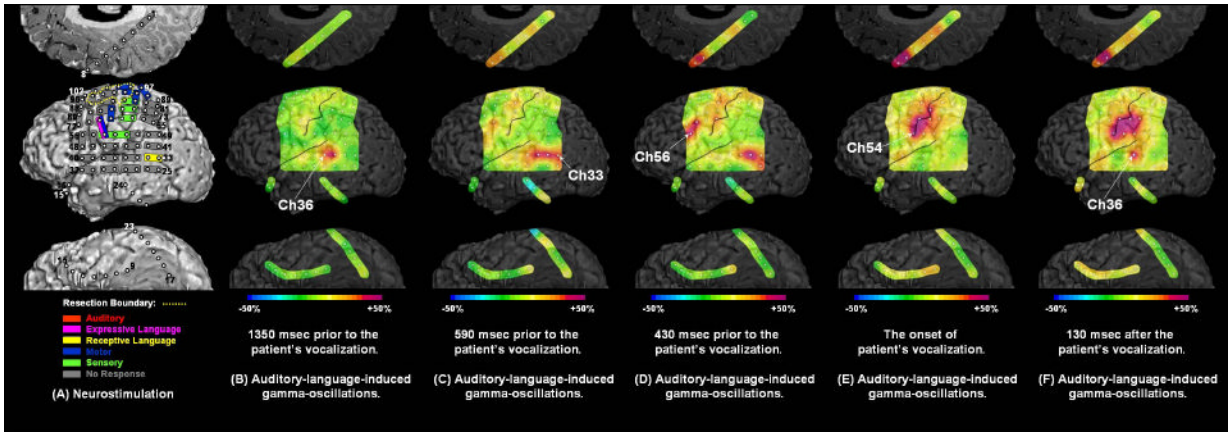



**Figure 1. Simultaneous Recording of ECoG and Vocal Sound Waves in Patient 1**

(A) An example of ECoG trace suitable for quantitative analysis is shown with a lowfrequency filter of 53-Hz and a high-frequency filter of 300-Hz. Vocal sound waves were simultaneously recorded with intracranial ECoG. The time-lock trigger was placed at the onset of patient's vocalization.

(B) Vocal sound wave on Cool Edit Pro Software is shown, and this was used to visually and audibly aid in the manual determination of the onset of the patient's vocalization.



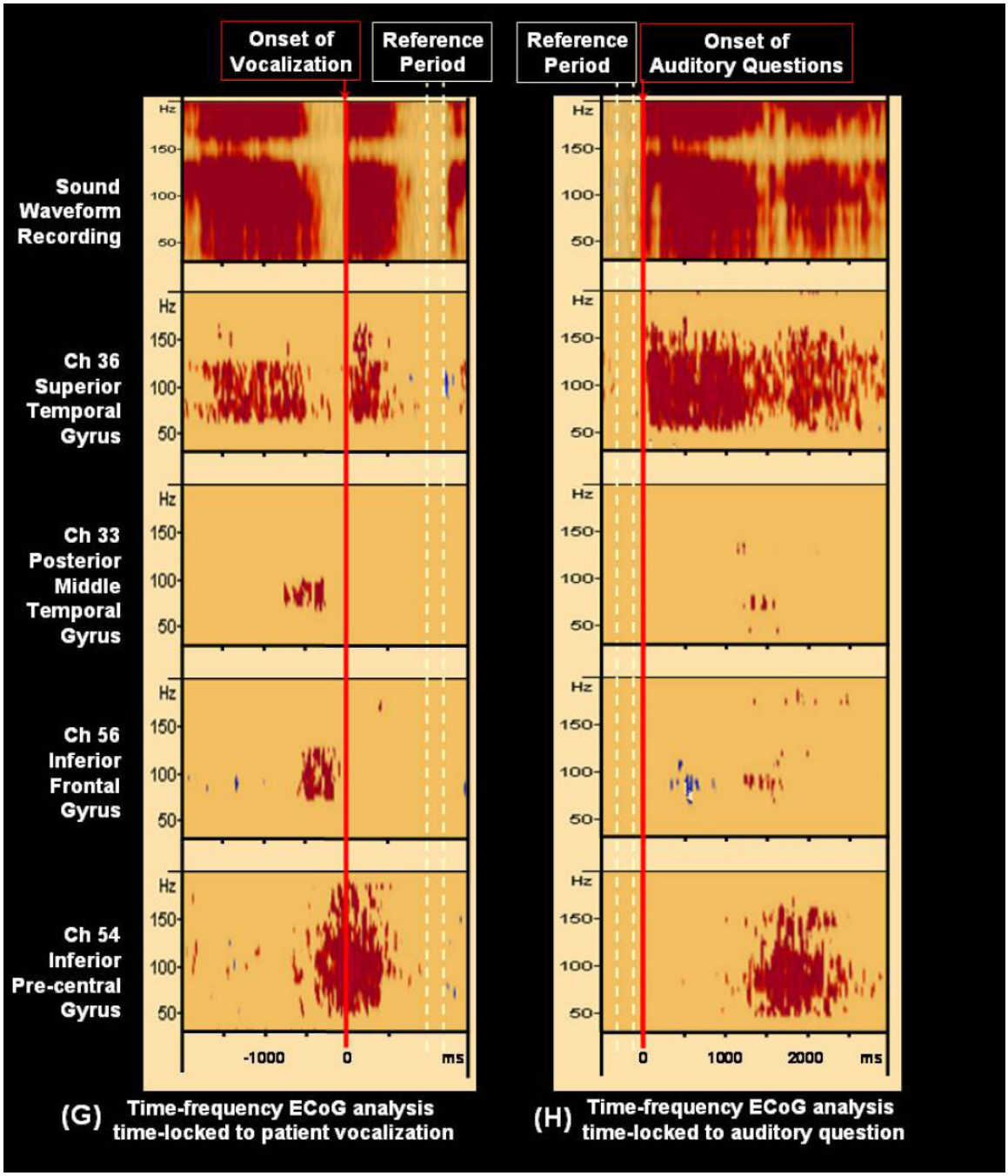



**Figure 2. Language Mapping in Patient 1**

(A) Neurostimulation: Stimulation of an electrode pair of the posterior temporal lobe (Ch33 & 34; denoted by a yellow box) induced language comprehension deficit. Stimulation of an electrode pair of the posterior frontal lobe (Ch54 & 70; denoted by a pink-blue box) resulted in pure speech arrest at 6 mA of stimulation and induced speech arrest associated with facial movement at 9 mA of stimulation. Stimulation of three electrode pairs on the post- and pre-central gyri (Ch53 & 54; 52 & 53; 67 & 68; denoted by green boxes) resulted in tingling of the mouth including the tongue. Stimulation of electrode pairs (Ch75 & 76; 83 & 84; denoted by green boxes) resulted in sensory responses involving the right upper extremity. Language function was not satisfactorily assessed in the following electrode sites, where neurostimulation

induced prominent motor responses and stimulation had to be prematurely terminated before completion of a question-and-answer trial. Facial movement was induced by stimulation of an electrode pair of the inferior portion of the pre-central gyrus (Ch69 & 77; denoted by a blue box), and motor responses involving the right upper extremity were induced by stimulation of electrode pairs of the superior portion of the pre- and post-central gyri (Ch83 & 91; 91 & 92; 90 & 97; 98 & 99; denoted by blue boxes). Surgical resection of the superior precentral gyrus and the superior premotor region resulted in worsening of hemiparesis in the right-sided upper extremity but no postoperative language deficits were noted.

(B - G) ECoG time-frequency analysis time-locked to patient's vocalization: This analytic method was designed to evaluate sequential brain activation associated with comprehension, word retrieval, and vocalization. A greater than 50% increase in 'gamma-range amplitude' (across 50- to 150-Hz frequency bands) was noted in the left superior temporal gyrus at 1350-msec prior to the patient's vocalization (B), in the left middle temporal gyrus at 590-msec prior to the patient's vocalization (C), in the left middle temporal gyrus, inferior frontal gyrus and superior frontal gyrus at 430-msec prior to the patient's vocalization (D), in the left superior frontal gyrus as well as pre- and postcentral gyri at the onset of patient's vocalization (E), and in the left superior temporal gyrus, superior frontal gyrus as well as pre- and post-central gyri at 130-msec after the patient's vocalization (F). (G) Sound waveform recording data showed no temporal overlap between the sound of auditory questions and that of patient's vocalization. Highfrequency gamma-augmentation began to involve the superior temporal gyrus (Ch 36) at 1,750-msec prior to the onset of patient's vocalization, the middle temporal gyrus (Ch 33) at 740-msec prior to the onset of patient's vocalization, the inferior frontal gyrus (Ch 56) at 510-msec prior to the onset of patient's vocalization, the inferior pre-central gyrus (Ch 54) at 470-msec prior to the patient's vocalization, and the superior temporal gyrus (Ch 36) at 70-msec after the onset of patient's vocalization.

(H) ECoG time-frequency analysis time-locked to auditory questions: This analytic method was designed to evaluate brain activation associated with the initiation of auditory question. Sound waveform recording data showed the evidence of temporal overlap between the sounds derived from auditory questions and patient's vocalization. Thus, high-frequency gamma augmentation in the superior temporal gyrus (Ch 36) was probably induced by both auditory questions and patient's vocalization at some point. The time-frequency matrixes for the entire subdural electrode sites are presented as supplementary data on the website.

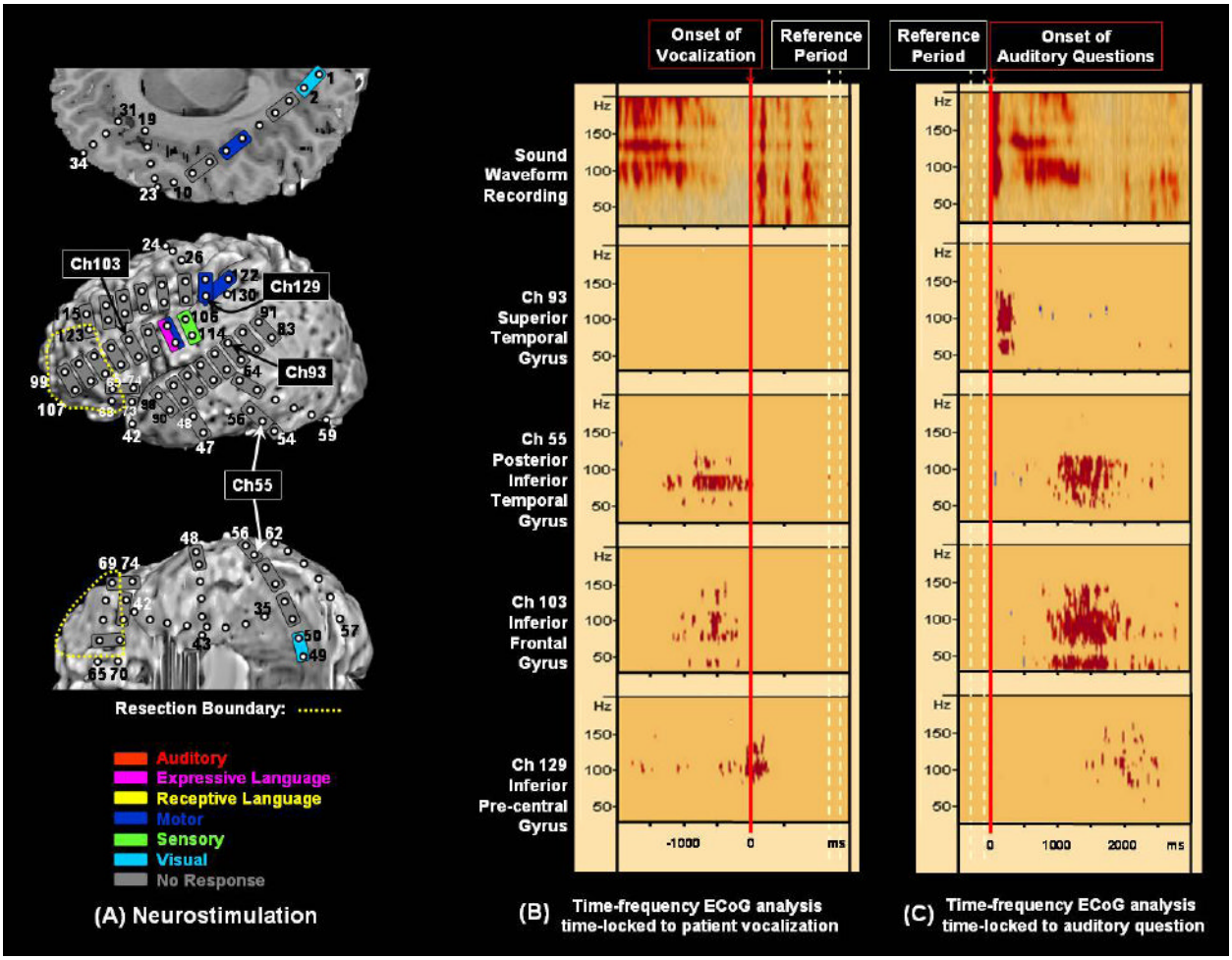



**Figure 3. Language Mapping in Patient 3**

(A) Neurostimulation: Stimulation of two electrodes pairs on the occipital lobe resulted in visual symptoms (Ch1 & 2; 49 & 50; denoted by light-blue boxes). Stimulation of an electrode pair of the inferior pre-central gyrus (Ch105 &113; denoted by a pink-blue box) induced speech arrest associated with throat movement. Stimulation of an electrode pair of the inferior post-central gyrus (Ch106 & 114; denoted by a green box) resulted in tingling of teeth. Language function was not satisfactorily assessed in the following electrode sites, where neurostimulation induced positive motor responses and stimulation had to be prematurely terminated before completion of a question-and-answer trial. Stimulation of an electrode pair of the pre- and post-central gyrus (Ch121 & 129; denoted by a blue box) resulted in movement of mouth. Stimulation of an electrode pair of the post-central gyrus (Ch122 & 129; denoted by a blue box) resulted in movement of the thumb. Stimulation of a pair of the medial frontal region (Ch6 & 7; denoted by a blue box) resulted in tonic extension of the bilateral upper extremities. (B) ECoG time-frequency analysis time-locked to patient's vocalization: This analytic method was designed to evaluate sequential brain activation associated with comprehension, word retrieval, and vocalization. No cortical activation represented as gamma-augmentation was observed in the superior temporal gyrus (Ch 93) during auditory questions. High-frequency gamma-augmentation began to involve the posterior inferior temporal gyrus (Ch 55) at 1,220-msec prior to the onset of patient's vocalization, the inferior frontal gyrus (Ch 103) at 590-msec prior to the onset of patient's vocalization, and the inferior pre-central gyrus (Ch 129) immediately prior to the patient's vocalization.

(C) ECoG time-frequency analysis time-locked to auditory questions: This analytic method was designed to evaluate brain activation associated with the initiation of auditory question. High-frequency gamma augmentation began to involve the left superior temporal gyrus (Ch 93) at 70-msec after the onset of auditory questions, the posterior inferior temporal gyrus (Ch 55) at 1,020-msec after the onset of auditory questions, and the inferior frontal gyrus (Ch 103) at 910-msec after the onset of auditory questions. The time-frequency matrixes for the entire subdural electrode sites are presented as supplementary data on the website.

**Table 1**

**Summary of Clinical Information**

F: Female. M: Male. Lt: Left. Rt: Right. CBZ: Carbamazepine. LEV: Levetiracetam. VGB: Vigabatrin. PHT: Phenytoin. OXC: Oxcarbazepine. ZNS: Zonisamide. VCI: Verbal Comprehension Index. N/A: Not Applicable. VIQ: Verbal IQ. Sz: Seizures. sGTC: Secondarily Generalized Tonic Clonic Seizures. F: Frontal. T: Temporal. O: Occipital. P: Parietal. C: Central. N/A: Not Applicable.

| Patients | Gender | Age (yr) | Antiepileptic mediations | Seizure semiology | Interictal spikes on scalp EEG | Ictal EEG onset on scalp EEG | Electrode placement | Seizure onset zones determined on ECoG | ECoG contacts | Histology |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 16 | CBZ, LEV | Focal Sz + sGTC | Diffuse, BiFrontal | N/A | Lt FPT | Lt F | 94 | Tumor |
| 2 | F | 10 | LEV | Focal Sz + sGTC | N/A | Lt F | Lt FPT | Lt F | 74 | Tumor |
| 3 | F | 9 | VGB, PHT | Focal Sz | Lt F, Lt T & Rt F | Lt F & Lt T | Lt FPTO | Lt F | 117 | Cortical Tubers |
| 4 | F | 7 | OXC, ZNS | Focal Sz + sGTC | Lt TPOC | Lt TPO | Lt POTF | Lt T; Lt F | 128 | Gliosis |

**Table 2**

**Behavioral Data**

F: Female. M: Male. Lt: Left. Rt: Right. VCI: Verbal Comprehension Index. N/A: Not Applicable. VIQ: Verbal IQ. SD: Standard Deviation. The presented data include: the mean and standard deviation of response latencies (the interval between the offset of auditory question and the onset of patient's vocalization; unit: msec) derived from the trials included into the ECoG analysis time-locked to patient's vocalization.

| Patients | Gender | Age (yr) | Handedness | VCI | VIQ | Wada test | Response time Mean +/- SD |
|---|---|---|---|---|---|---|---|
| 1 | M | 16 | Rt | 81 | N/A | N/A | 529 +/- 134 |
| 2 | F | 10 | Rt | 85 | N/A | N/A | 661 +/- 156 |
| 3 | F | 9 | Rt | 99 | N/A | Lt Language Dominance | 669 +/- 217 |
| 4 | F | 7 | Lt | N/A | 75 | N/A | 942 +/- 275 |

**Table 3**

**Spatial, Temporal and Frequency Characteristics of Induced Gamma-Augmentation**

(A) Gamma-augmentation relative to the onset of patient's vocalization, and (B) Gamma-augmentation relative to 'the onset of auditory question'. The presented data include: the number of sites showing significant gamma-augmentation in a continuous array spanning at least 20-Hz in width and at least 20-msec in duration as well as the frequency range and latency of such gamma-augmentation.

| **A:** | **Spatial, Temporal and Frequency Characteristics of Gamma-Augmentation Relative to 'the Onset of Patient's Vocalization'** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient** | **Number of trials included into the statistical Analysis** | **Superior temporal gyrus** | **Middle-inferior temporal gyri** | **Inferior frontal gyrus** | **Superior-frontal gyrus & Cingulate gyrus** | **Medial temporal lobe structure** | **Pre- and Post-central gyri** |
| **1** | 42 | 3 sites; 65 to 165 Hz; -1750 to -320 msec & +70 to +520 msec | 2 sites; 70 to 100 Hz; -740 to -280 msec | 2 sites; 75 to 125 Hz; -510 to -160 msec | 3 sites; 55 to 155 Hz; -700 to +500 msec | 1 site; 90 to 110 Hz; -70 to -20 msec | 15 sites; 50 to 185 Hz; -470 to +500 msec |
| **2** | 44 | 2 sites; 75 to 110 Hz; -1580 to -720 msec & -20 to +700 msec | Not covered | 2 sites; 40 to 105 Hz; -570 to -60 msec | 2 sites; 65 to 100 Hz; -610 to -400 msec | 1 site; 80 to 100 Hz; -510 to -280 msec | 7 sites; 65 to 190 Hz; -550 to +630 msec |
| **3** | 40 | 0 site | 1 site; 75 to 125 Hz; -1220 to -150 msec | 2 sites; 40 - 140 Hz; -590 to -150 msec | 2 sites; 65 - 115 Hz; -980 to -80 msec | 0 site | 2 sites; 70 to 145 Hz; -210 to +350 msec |
| **4** | 6 | 0 site | 0 site | 0 site | 0 site | 0 site | 0 site |
| B: | Spatial, Temporal and Frequency Characteristics of Gamma-Augmentation Relative to 'the Onset of Auditory Question' | | | | | | |
| Patient | Number of trials included into the statistical analysis | Superior temporal gyrus | Middle-inferior temporal gyri | Inferior frontal gyrus | Superior-frontal gyrus & Cingulate gyrus | Medial temporal lobe structure | Pre- and Post-central gyri |
| **1** | 51 | 8 sites; 55 to 165 Hz; +30 to +2900 msec | 1 site; 65 to 105 Hz; +1260 to +1770 msec | 0 site | 3 sites; 60 to 150 Hz; +1050 to +2500 msec; | 0 site | 10 sites; 50 to 170 Hz; +990 to +2480 msec |
| **2** | 38 | 3 sites; 65 to 110 Hz; +90 to +960 msec & +1510 to +2800 msec | Not covered | 0 site | 1 site; 75 to 130 Hz; +1000 to +1360 msec | 0 site | 2 sites; 70 to 190 Hz; +1410 to +2500 msec |
| **3** | 56 | 3 sites; 55 to 140 Hz; +70 to +1970 msec | 3 sites; 50 to 120 Hz; +1020 to +1830 msec | 2 sites; 35 to 145 Hz; +910 to +1920 msec | 3 sites; 50 to 150 Hz; +910 to +2020 msec; | 1 site; 70 to 110 Hz; +1310 to +1960 msec | 4 sites; 65 to 160 Hz; +1030 to +2900 msec |
| **4** | 28 | 1 site; 75 to 100 Hz; +320 to +1210 msec | 0 site | 0 site | 0 site | 0 site | 0 site |