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Cortical gamma-oscillations modulated by listening and overt repetition of phonemes

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SUMMARY

Both superior temporal gyrus and inferior Rolandic area have been reported to be involved in perception and production of speech in humans. Here, we determined *how* these cortical structures were activated by listening and subsequent overt articulation of syllables, by measuring event-related gamma-oscillations as quantitative measures of cortical activation. Fifteen subjects were presented an auditory syllable consisting of either 'fee [fi:]', 'faa [f**ɑ**:]', 'hee [hi:]', or 'haa [h**ɑ**:]', and were instructed to overtly repeat each given syllable. Gamma-oscillations in the superior temporal gyrus were highly augmented during syllable-presentation, least augmented at the onset of syllable-articulation, and again highly augmented following syllable-articulation. Gamma-oscillations were augmented in the inferior Rolandic area prior to and during syllable-articulation with the onset and peak occurring earlier in the left side. Subsets of the inferior Rolandic sites, more frequently on the left side, showed differential gamma-augmentation elicited by articulation of phoneme [f] more than [h] or phoneme [i:] more than [**ɑ**:]. Our observations suggest that the superior temporal gyrus may be active when externally-presented or articulated auditory stimuli are present, and may be minimally active when articulation is about to be initiated. Our novel observation of phoneme-specific differential gamma-augmentation in the inferior Rolandic area may be partially attributed to the mouth position during phoneme-articulation. Our observations support the hypothesis that positioning of the mouth to articulate phonemes is predominantly driven and/or monitored by the primary sensorimotor area on the left side.

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Keywords

language; epilepsy surgery; electroencephalography (EEG); electrocorticography (ECoG); in-vivo animation

INTRODUCTION

In human language, each phoneme is produced by vibration of the vocal cord in the throat along with each distinct position of the mouth: such as lip, tongue, teeth, and upper palate (Greenberg, 1969). Previous neuroimaging studies using functional MRI (fMRI) and positron emission tomography (PET) have localized *what* cortical circuits are involved in perception and production of speech; it was reported that such cortical circuits include the superior temporal gyri as well as the inferior portion of Rolandic area (i.e.: pre- and post-central gyri) bilaterally with larger extent in the left hemisphere (Zatorre et al., 1992; Wilson et al., 2004; McNealy et al., 2006; Pulvermüller et al., 2006; Dhanjal et al., 2008). The dynamics of speech-related cortical activation have been less clarified by such neuroimaging studies due to the limited temporal resolution. Taking into account the tight correlation between increased BOLD signals on fMRI and event-related gamma-oscillations (>50Hz) on electrocorticography (ECoG) (Niessing et al., 2005), we hypothesized that some of the unanswered questions could be addressed by studies using ECoG, of which temporal resolution is 10 msec or less (Fukuda et al., 2008). We also hypothesized that the electrophysiological observations in ECoG studies could provide external validation for the findings reported by previous neuroimaging studies. Benefits of ECoG recording also include: (i) minimal artifacts derived from cranial muscles or head movement during overt vocalization (Sinai et al., 2005; Brown et al., 2008; Towle et al., 2008), and (ii) a better signal-to-noise ratio compared to scalp electroencephalography (EEG) and magnetoencephalography (MEG), which record cortical signals from outside of the scalp (Dalal et al., 2009).

In our institute, extraoperative ECoG recording is performed in young patients with focal epilepsy following subdural electrode placement and prior to removal of the presumed epileptogenic zone (Asano et al., 2009a), and has provided us with *unique* opportunities to monitor neuronal activities in human cerebral cortex. In the present study, subjects were presented auditory-syllables and were requested to repeat each given syllable overtly during extraoperative ECoG recording; event-related gamma-oscillations (30 – 200 Hz) were then measured as quantitative measures of cortical activation. It has been generally believed that augmentation of gamma-oscillations represents cortical activation (Pfurtscheller and Lopes da Silva, 1999; Tallon-Baudry and Bertrand, 1999; Ray et al., 2008a), whereas attenuation of gamma-oscillations represents cortical deactivation (Towle et al., 2008; Asano et al., 2009b). Here, we addressed the following specific hypotheses. (i) We hypothesized that gamma-oscillations in the superior temporal gyrus would be augmented during presentation of auditory syllables and again augmented following the onset of syllable-articulation. (ii) We hypothesized that gamma-oscillations would be augmented in the inferior Rolandic area prior to and during syllable-articulation with the onset and peak of gamma-augmentation occurring earlier on the left side. (iii) We hypothesized that articulation of specific phonemes would differentially elicit gamma-augmentation in the inferior Rolandic area more frequently in the left side. (iv) We hypothesized that electrical neurostimulation of the sites showing large language-event-related gamma-augmentation would elicit concordant symptoms more frequently than would neurostimulation of the remaining sites.

MATERIALS and METHODS

Subjects

The inclusion criteria of the present study consisted of: (i) age 4 years or above, (ii) a two-stage epilepsy surgery using chronic subdural ECoG recording in Children's Hospital of Michigan, Detroit, between January 2007 and August 2008, (iii) subdural electrodes chronically implanted on the inferior Rolandic area (within 4 cm from the Sylvian fissure) as well as a posterior portion of the superior temporal gyrus (4 cm or more posterior from the temporal pole) on either hemisphere, (iv) functional cortical mapping for the primary auditory area as well as primary sensorimotor area using measurement of event-related gamma-oscillations associated with listening and subsequent articulation of syllables, and The exclusion criteria consisted of: (i) the presence of massive brain malformations (such as large porencephaly, perisylvian polymicrogyria or hemimegalencephaly) which are known to confound the anatomical landmarks for the central sulcus and sylvian fissure, (ii) subsequent surgical resection involving the areas showing seizure onset from either the posterior superior temporal gyrus or inferior Rolandic area, and (iii) the presence of epilepsia partialis continua. We studied a consecutive series of 15 native English-speaking patients with a diagnosis of medically-uncontrolled focal seizures (age range: 7 - 18 years; 10 females) who satisfied both inclusion and exclusion criteria (Table S1 [supplementary data on the website]). Speech delays were noted in patients 1 and 13, and gross confrontation revealed a left-sided visual-field defect in patient 7 (Table S2 [supplementary data on the website]). The study has been approved by the Institutional Review Board at Wayne State University, and written informed consent was obtained from the guardians of all subjects.

Subdural electrode placement

For continuous extraoperative ECoG recording and subsequent functional cortical mapping, platinum grid electrodes were surgically implanted, as previously described (Fukuda et al., 2008; Asano et al., 2009a). The total number of electrode contacts in each subject ranged from 64 to 150. Subdural electrodes were placed on the left hemisphere in patients 1 - 6 and on the right hemisphere in patients 7 -15. There was no significant side-difference in the number of sampled sites per patient in the posterior portion of superior temporal gyrus (4 cm or more posterior from the temporal pole) (mean: 8.3 sites/patient on the left and 8.4 sites/patient on the right; p=0.9 on Mann-Whitney U Test) or in the inferior Rolandic area (0 - 4 cm from the Sylvian fissure) (mean: 10.3 on the left and 10.7 on the right; p=0.6).

Coregistration of subdural electrodes to the individual three-dimensional MRI

MRI including a T1-weighted volumetric spoiled gradient echo image as well as fluid-attenuated inversion recovery image was obtained preoperatively (Asano et al., 2009b). 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 directly defined on the brain surface, as previously described (von Stockhausen et al., 1997; Muzik et al., 2007). The central sulcus, the pre-central gyrus and post-central gyrus were identified according to anatomical MRI landmarks (Berger et al., 1990; Yousry et al., 1997), as previously described (Fukuda et al., 2008).

Extraoperative video-ECoG recording

Extraoperative video-ECoG recordings were obtained, using a 192-channel Nihon Kohden Neurofax 1100A Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA); the sampling rate was set at 1,000 Hz with the amplifier band pass at 0.08 - 300 Hz (Asano et al.,

2009b). The averaged voltage of ECoG signals derived from the fifth and sixth electrodes (system reference potential) was used as the original reference. ECoG signals were then re-montaged to a common average reference, as previously described by a number of investigators (Sinai et al., 2005; Miller et al., 2007; Brown et al., 2008; Towle et al., 2008). Advantage and limitation of usage of a common average reference for measurement of event-related gamma-oscillations were previously discussed (Crone et al., 2001a; Asano et al., 2009b). Channels contaminated with large interictal epileptiform discharges or artifacts were excluded from the average reference (Fukuda et al., 2008). No notch filter was used for further analysis in any subjects. Antiepileptic medications were discontinued or reduced during ECoG monitoring until a sufficient number of habitual seizures were captured. Locations of seizure onset zones are described in Table S1 (supplementary data on the website).

Syllable-repetition task

None of the subjects had a seizure within two hours prior to the syllable-repetition task. The task was employed in a sound-attenuated room, and each subject was awake, unsedated, and comfortably seated on the bed during the tasks. Before the syllable-repetition task was initiated, the intensity of auditory-syllable was adjusted to a comfortable hearing level (Towle et al., 2008). Each subject was presented an auditory-syllable consisting of either ‘fee [fi:]’, ‘faa [f**ɑ**:]’, ‘hee [hi:]’, or ‘haa [h**ɑ**:]’ 80 times (Stecker et al., 2006), and was instructed to overtly repeat each given syllable. Each auditory-syllable was given 20 times in a pseudorandom sequence via two open-field speakers with an approximate intensity of 65 - 70 dB and with inter-stimulus intervals randomized between 3,300 and 3,700 msec.

The presented and repeated syllables were 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 [supplementary data on the website]). The onsets of presented and repeated syllables were marked on ECoG traces, as previously described (Brown et al., 2008).

Measurement of ECoG amplitude modulations elicited by the syllable-repetition task

Time-frequency analysis of gamma-oscillations relative to ‘the onset of audibly-presented syllable’—This time-frequency analysis was designed to evaluate cortical activation for acoustic and phonetic perception of auditorily-presented syllables and to identify a portion of the primary auditory area presumably located in the superior temporal gyrus on the recorded hemisphere. We specifically determined whether gamma-oscillations in the superior temporal gyrus were significantly augmented following presentation of auditory-syllables, and described the spatial and temporal characteristics of such gamma-modulations in the superior temporal gyrus. Since the latencies between presentation of auditory-syllables and articulation of given syllables were not uniform across trials, this analytic method was not designed to evaluate cortical activation associated with movement execution to articulate syllables, as suggested in our previous study (Brown et al., 2008). ECoG amplitude modulations elicited by auditorily-presented syllables were evaluated using the trigger point set at the onset of all four types of syllables.

The inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: at least 1,000-msec of silence (i.e.: no auditory noise such as coughing) occurred prior to the onset of auditorily-presented syllables. The exclusion criteria included: i) ECoG trace was affected by artifacts derived from prominent body movement; ii) ECoG trace was affected by electrographic seizures; and iii) ECoG trace derived from the superior temporal gyrus was affected by runs of interictal epileptiform discharges lasting longer than 3 seconds. Exclusion of ECoG epochs was performed by an investigator (M.F.) while being blinded to the results of time-frequency analysis; all ECoG epochs (up to 80 epochs) which satisfied all of the

inclusion and exclusion criteria were utilized for the time-frequency ECoG analysis described below. The number of trials per task in the present study was larger than those in our previous studies of event-related gamma-oscillations (Brown et al., 2008; Asano et al., 2009b).

Time-frequency analysis was performed using the BESA® EEG V.5.1.8 software (MEGIS Software GmbH, Gräfelfing, Germany); each suitable ECoG trial was transformed into the time-frequency domain using complex demodulation technique (Papp and Ktonas, 1977; Hoechstetter et al., 2004; Fan et al., 2007; Brown et al., 2008; Fukuda et al., 2008; Asano et al., 2009b). In this 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 filter of Gaussian shape. Details of the complex demodulation technique for time-frequency transformation are described elsewhere (Papp and Ktonas, 1977; Hoechstetter et al., 2004). 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 syllable-presentation). In this study, only the amplitude (also known as 'square root of power'), averaged across all trials, was used for further analysis. It has been reported that a percent change of 'amplitude' is easier to visually relate to the raw signal record compared to that of 'power' (da Silva, 1999). Time-frequency transformation was performed for frequencies between 30- and 200-Hz and latencies between −1,000 msec and +2,000 msec relative to the onset of auditorily-presented syllables, in steps of 5-Hz and 10-msec. This corresponded to a time-frequency resolution of +/−9.9 Hz and +/−22.2 msec (50% amplitude drop of the finite impulse response 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 of 800 msec in duration between −1,000 and −200 msec relative to the onset of auditorily-presented syllables. This parameter is commonly termed "event-related synchronization and desynchronization" (Pfurtscheller et al., 1977; Pfurtscheller and Lopes da Silva, 1999), whereas a less suggestive terminology is "temporal spectral evolution" (TSE) (Salmelin and Hari, 1994).

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 (Davison and Hinkley, 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 10,500 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 significant attenuation of amplitude, and red color indicated significant augmentation of amplitude in the corresponding time-frequency bin relative to the reference period.

As described in our previous studies (Brown et al., 2008; Asano et al., 2009b), an additional correction for testing in multiple electrodes (the number of subdural electrodes ranged from 64 to 150 across subjects) was employed. TSE values in a given electrode were declared to be statistically significant only if a minimum of eight voxels in the 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 those with very short durations (less than 20-msec). Some previous studies *using scalp EEG recording* showed augmentation of a narrow-range gamma-band oscillations around 40 Hz (Tallon-Baudry et al., 1996), whereas event-related gamma-modulations observed in studies *using intracranial ECoG recording* commonly involved wide-range frequency bands ranging at least 20-Hz in width (Tallon-Baudry et al., 2005; Brown et al., 2008; Fukuda et al., 2008; Asano et al., 2009b).

Time-frequency analysis of gamma-oscillations relative to 'the onset of syllable-articulation'—ECoG amplitude modulations were also evaluated using the trigger point set at the onset of articulated syllables, using an approach similar to that previously reported (Brown et al., 2008). This analytic method was designed to evaluate sequential cortical activation consisting of movement execution to articulate given syllables and perception of articulated syllables. Here, we specifically determined whether gamma-oscillations were augmented in the inferior Rolandic area prior to and during articulation of syllables. We also determined whether 'gamma-oscillations in the superior temporal gyrus augmented by auditory-syllables' returned to the baseline level around the onset of syllable-articulation and then augmented again following syllable-articulation.

Similarly employed in our previous study (Brown et al., 2008), the inclusion criteria defining ECoG epochs suitable for this time-frequency analysis included: i) the subject articulated a correct syllable, and ii) the variability of delay between the onset of audibly-presented syllables and the onset of articulated syllables must be within 1,000 msec across trials; and iii) a period of silence lasting 800 msec must be available as a reference period between +1,200 to +2,000 msec relative to the onset of articulated syllables. 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 inferior Rolandic area was affected by runs of interictal epileptiform discharges. All 3,000-msec ECoG epochs (starting −1,000 msec and ending +2,000 msec relative to the onset of articulated syllables) which satisfied all of the inclusion and exclusion criteria were utilized for the time-frequency ECoG analysis. Alteration of ECoG amplitude was determined using the statistical approach as described above.

Determination of gamma-oscillations differentially modulated by articulation of a specific phoneme

We determined whether articulation of a specific phoneme differentially modulated gamma-oscillations in the inferior Rolandic area. Using ECoG traces relative to the onset of syllable-articulation, we compared ECoG amplitude between 40 trials containing phoneme [f] and the other 40 containing phoneme [h]; we also compared ECoG amplitude between trials containing phoneme [i:] and those containing phoneme [**ɑ**:]. As described above, a given electrode was declared to have significant gamma-oscillations differentially augmented by articulation of a specific phoneme, only if TSE values differed between two types of trials in a minimum of eight voxels in the gamma-band range in a continuous array spanning at least 20-Hz in width and at least 20-msec in duration.

Similarly, using ECoG traces relative to the onset of presentation of auditory-syllables, we determined whether listening to a specific phoneme differentially modulated gamma-oscillations in the superior temporal gyrus.

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 animate *'when'*, *'where'* and *'how many fold'* gamma-oscillations were increased or decreased, 'gamma-range amplitude' (defined as the spectral amplitude averaged across 50- to 150-Hz frequency bands

and normalized to that of the reference period) was sequentially delineated on the individual three-dimensional MRI (Figure 1; Video S1 [supplementary data on the website]), using a method previously described (Brown et al., 2008;Asano et al., 2009b). 'Gamma-range amplitude' was calculated without a frequency band at 60Hz if visual inspection revealed a 60-Hz artifact peak on the amplitude spectral curve for all subdural electrodes. 'Gamma-range amplitude' (unit: %) 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 the interpolated topography map of 'gamma-range amplitude' at each 10-msec epoch was accurately superimposed to the individual three-dimensional MRI. This procedure yielded a movie file showing a sequential alteration of gamma-oscillations elicited by the syllable-repetition task.

In order to delineate *'when', 'where'* and *'at what frequency band'* significant alteration of spectral 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 1 and 2).

Functional cortical mapping using electrical neurostimulation

Functional cortical mapping by electrical neurostimulation was performed during extraoperative ECoG recording, using a method similar to those described previously (Crone et al., 1998; Miller et al., 2007; Brown et al., 2008; Asano et al., 2009b). A pulse-train of electrical stimuli was delivered using the Grass S88 constant-current stimulator (Astro-Med, Inc, West Warwick, RI, USA); clinical responses associated with stimulations were observed by at least two investigators blinded to the results of time-frequency ECoG analyses. In order to minimize the risk of a subject feeling scared or overwhelmed, each subject was informed that she/he might have a temporary sensorimotor, auditory, visual or language symptom, prior to the initiation of neurostimulation study. Each subject was also aware of the timing of each stimulation trial. Informing subjects of a potential symptom prior to neurostimulation may increase the risk of biased anticipation, and this could be an issue when clinical decisions solely rely on subjective percepts. In order to reduce (but not eliminate) such a bias, the subjects were informed of the list of symptoms (sensorimotor, auditory, visual or language symptom) rather than told of a specifically anticipated symptom.

To determine the presence of after-discharges, video-ECoG was recorded continuously during the procedure. To minimize the risk of stimulation-induced seizures, a loading dose of phenytoin (20 mg/kg) was administered intravenously prior to the mapping session (Fukuda et al., 2008). We recognize that phenytoin, one of the sodium channel blockers, may affect the findings of neurostimulation and that failure to elicit clinical symptoms by neurostimulation, if any, could be partially attributed to the acute effect of phenytoin given prior to neurostimulation.

Subdural electrode pairs were stimulated by an electrical pulse-train of 5-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. When the subject perceived positive auditory symptoms elicited by neurostimulation, she/he was asked to describe the nature of such auditory perception. During each period of neurostimulation, each subject with ECoG sampled from the left hemisphere was asked to answer a brief question verbally given by a neuropsychologist (R.R.). When the subject was unable to talk or answer, she/he was asked to provide the reason (Brown et al., 2008). Brain regions at which stimulation consistently elicited a clinical response (at least twice in a row) were declared 'eloquent for that function' in the present study. When after-discharge without an observed clinical response or when neither clinical response nor after-discharge was elicited by the maximally-intense

stimuli, the brain region was declared ‘not proven eloquent’. When both clinical response and after-discharges occurred, another pulse-train of the same or 1-mA smaller intensity was used until either clinical response or after-discharge failed to develop.

We specifically determined whether auditory or receptive language symptoms were elicited by electrical neurostimulation of the posterior superior temporal gyrus showing the largest gamma-augmentation elicited by auditory-syllables, compared to neurostimulation of the remaining sites. Similarly, we determined whether sensorimotor symptoms involving the mouth or throat were elicited by electrical neurostimulation of the inferior Rolandic sites showing the largest articulation-related gamma-augmentation more frequently compared to stimulation of the remaining sites. We were aware that sensitivity of electrical neurostimulation is not as good in children as in adults and that failure to elicit a clinical symptom using neurostimulation does not prove the absence of eloquent function in the stimulated site (Ojemann et al., 2003; Haseeb et al., 2007; Schevon et al., 2007). Nevertheless, statistically significant concordance between the results of time-frequency ECoG analysis and electrical neurostimulation, if present, can provide validation to our methodology for localization of the presumed auditory-language areas as well as the primary sensorimotor area for the mouth and throat.

RESULTS

Behavioral data

All subjects satisfactorily completed the syllable-repetition task. There was no significant difference between the mean or standard deviation (SD) of reaction times between subjects whose ECoG was sampled from the left hemisphere (mean reaction time: 989 msec; SD: 225 msec on average) and those from the right hemisphere (i.e.: mean reaction time: 1019 msec; SD: 198 msec on average) ($p>0.4$ on Mann-Whitney U Test). Reaction time was defined as the period between the onset of auditorily-presented syllables and the onset of articulated syllables. There was no significant side difference between the number of trials included into time-frequency ECoG analysis relative to the onset of syllable-articulation (mean: 77.7 in the left and 76.4 in the right hemisphere) ($p>0.4$ on Mann-Whitney U Test).

Gamma-augmentation was elicited in the superior temporal gyrus following presentation of auditory-syllables

Time-frequency ECoG analysis of each individual relative to the onset of syllable-presentation demonstrated significant gamma-augmentation in the temporal neocortex in the recorded hemisphere in all 15 patients. The total number of electrode sites showing significant gamma-augmentation following syllable-presentation was 73 sites (mean across the 15 subjects: 4.9 sites); 67 sites were located on the superior temporal gyrus and 6 on the superior temporal sulcus. There was no significant difference in the number of sites showing significant gamma-augmentation between the left and right hemispheres (mean: 3.8 sites on the left and 5.6 sites on the right; $p=0.3$ on Mann-Whitney U Test). The electrode site showing the largest ‘gamma-range amplitude’ (defined as ‘the center of syllable-related gamma-oscillations’) was located in the superior temporal gyrus at 1.7 cm (SD: 0.7 cm) posterior from the bottom of central sulcus on average across the 15 patients. There was no significant difference in the distance between ‘the center of syllable-related gamma-oscillations’ and the bottom of central sulcus between the left and right hemispheres ($p=0.7$ on Mann-Whitney U Test). The maximum peak value of ‘gamma-range amplitude’ in ‘*the center of syllable-related gamma-oscillations*’ was 92% on average across the 15 patients (SD: 53%). Gamma-augmentation in ‘*the center of syllable-related gamma-oscillations*’ reached the predefined significant level at +87 msec (SD: 63 msec) on average, and the peak latency of ‘gamma-range amplitude’ was +257 msec (SD:

70 msec) on average. There was no significant difference in the peak amplitude, onset latency or peak latency between the left and right sides ($p>0.1$ on Mann-Whitney U Test).

Electrical neurostimulation of an electrode pair including '*the center of syllable-related gamma-oscillations*' was performed in all patients. Neurostimulation of 4 of the 15 pairs including '*the center of syllable-related gamma-oscillations*' elicited positive auditory symptoms consisting of auditory-tones in patients 2, 9, 11 and 15 (Table S3 [supplementary data on the website]). On the other hand, neurostimulation of 5 of the remaining 515 pairs elicited congruent clinical symptoms; auditory symptoms were elicited in a single pair (patient 11) and receptive language impairment in 4 pairs (patients 3 - 6). Thus, we found that neurostimulation of electrode pairs including '*the center of syllable-related gamma-oscillations*' elicited either auditory or receptive language symptom 27 times more frequently compared to that of the remaining pairs ($p<0.0001$ on chi-square test).

Gamma-augmentation was also elicited in the superior temporal gyrus following articulation of syllables

Time-frequency analysis of each individual's ECoG relative to the onset of syllable-articulation demonstrated significant gamma-augmentation in the superior temporal gyrus in the recorded hemisphere in 13 of the 15 patients (all subjects except for patients 3 and 6 [Table S3 [supplementary data on the website]). The total number of electrode sites showing significant gamma-augmentation following presentation of auditory-syllables was 42 sites (mean across the 15 patients: 2.8 sites); 37 sites were on the superior temporal gyrus and 5 on the superior temporal sulcus. There was no significant difference in the number of sites showing significant gamma-augmentation between the left and right hemispheres (mean: 2.7 sites on the left and 2.9 sites on the right; $p=0.8$ on Mann-Whitney U Test). The number of electrode sites showing significant gamma-augmentation elicited by articulated syllables was smaller than that elicited by auditorily-presented syllables ($p<0.003$ on Wilcoxon-Signed Ranks Test). The electrode site showing the largest 'gamma-range amplitude' (defined as 'the center of syllable-articulation-related gamma-oscillations') was identical to '*the center of syllable-related gamma-oscillations*' in 9 of the 13 subjects, and located within 2 cm anterior from '*the center of syllable-related gamma-oscillations*' in the remaining 4 subjects. The maximum peak value of 'gamma-range amplitude' in 'the center of syllable-articulation-related gamma-oscillations' was 49% on average across the 13 subjects (SD: 21%) and smaller than that elicited by externally-presented syllables ($p=0.001$ on Wilcoxon Signed Ranks Test). Gamma-augmentation in 'the center of syllable-articulation-related gamma-oscillations' reached significant level at +165 msec after syllable-articulation (SD: 96 msec) on average, and the peak latency of 'gamma-range amplitude' was +380 msec (SD: 84 msec) on average. There was no significant difference in the peak amplitude, onset latency or peak latency between the left and right centers of syllable-articulation-related gamma-oscillations among the above-mentioned 13 subjects ($p>0.3$ on Mann-Whitney U Test).

Gamma-augmentation in the presumed primary auditory cortex was minimal around the onset of syllable-articulation

Time frequency analysis of *each individual's ECoG* relative to the onset of syllable-articulation demonstrated that gamma-augmentation in '*the center of syllable-related gamma-oscillations*' failed to maintain the predefined significant level around the onset of syllable-articulation in all 15 subjects and reached significant level following syllable-articulation in 13 subjects. On the other hand, *group analysis* of 15 subjects together demonstrated that 'gamma-range amplitude' in '*the center of syllable-related gamma-oscillations*' was minimally increased around the onset of syllable-articulation and never returned to the baseline level (Figure 3A).

Gamma-augmentation in the inferior Rolandic area elicited by syllable-articulation

Time-frequency analysis of each individual's ECoG relative to the onset of syllable-articulation demonstrated that articulation-movement elicited significant gamma-augmentation in the inferior Rolandic area in all 15 subjects (Table S4 [supplementary data on the website]); the electrode site showing the largest 'gamma-range amplitude' (defined as 'the center of articulation-related gamma-oscillations') was located in the pre-central gyrus in 8 subjects, post-central gyrus in 3 subjects and on the central sulcus in 4 subjects. 'The center of articulation-related gamma-oscillations' was located 2.3 cm (SD: 1.0 cm) superior from the sylvian fissure on average. The maximum peak value of 'gamma-range amplitude' in 'the center of articulation-related gamma-oscillations' was 62% on average (SD: 33%). There was no significant difference in the peak 'gamma-range amplitude' between the left and right sides (p=0.8 on Mann-Whitney U Test).

Analysis of each individual's ECoG demonstrated that gamma-augmentation in 'the center of articulation-related gamma-oscillations' reached significant level at −241 msec on average (SD: 214 msec) relative to the onset of syllable-articulation, and the peak latency of 'gamma-range amplitude' was +135 msec (SD: 153 msec) on average. Gamma-augmentation reached significant level earlier on the left side compared to the right side (mean onset latency: −358 msec on the left and −163 msec on the right side; p=0.04 on Mann-Whitney U Test), and 'gamma-range amplitude' reached the peak value earlier on the left side compared to the right (mean peak latency: +27 msec on the left and +207 msec on the right side; p=0.02 on Mann-Whitney U Test). In addition to analyses of each individual's ECoG, group analysis of the 15 subjects was also performed; the sequential change of 'gamma-range amplitude' in 'the center of articulation-related gamma-oscillations' is demonstrated in Figure 3B. It was demonstrated that gamma-augmentation in the inferior Rolandic area was preceded by that in the superior temporal gyrus.

Electrical neurostimulation of an electrode pair including 'the center of articulation-related gamma-oscillations' was performed in all 15 subjects. Neurostimulation of 14 of the 15 pairs including 'the center of articulation-related gamma-oscillations' elicited sensorimotor symptoms involving the mouth (n = 11) or throat (n = 3; patients 10, 11 and 13). On the other hand, neurostimulation of 38 of the total of 515 pairs other than 'the center of articulation-related gamma-oscillations' elicited sensorimotor symptoms involving the mouth or throat. The chi-square test indicated that the chance of neurostimulation of pairs including 'the center of articulation-related gamma-oscillations' eliciting sensorimotor symptoms involving the mouth or throat was 13 times higher than that of the remaining pairs (p<0.0001 on chi-square test).

Gamma-augmentation was differentially elicited by articulation of specific phonemes

A total of 13 inferior Rolandic sites revealed differential gamma-augmentation more intensely elicited by articulation of phoneme [f] than that of phoneme [h]; such differential gamma-augmentation was noted in 5 of the 6 subjects with ECoG sampled from the left hemisphere and in 2 of the remaining 9 subjects (Figures 1, 2 and 3). Similarly, two inferior Rolandic sites (one in the left and the other in the right side) revealed differential gamma-augmentation more intensely elicited by articulation of phoneme [i:] than that of phoneme [**ɑ**:] (Table S5 [supplementary data on the website]). Phoneme-specific differential gamma-augmentation was more frequently observed in subjects with ECoG sampled from the left compared to the right side (p=0.04 on Fisher's Exact Probability Test). Phoneme-specific differential gamma-augmentation was noted in 10 of the 62 left inferior Rolandic sites and in 5 of the 96 on the right. After taking into account the number of electrode sites sampled from the inferior Rolandic area on each hemisphere, phoneme-specific differential gamma-augmentation was still found to be more frequent in the left compared to the right side (p=0.04 on chi-square test). Such

phoneme-specific differential gamma-augmentation was noted 23 mm superior from the Sylvian fissure on average on the left side and 9 mm superior from it on average on the right side; there was a significant difference in the distance from the Sylvian fissure between the left and right Rolandic sites showing phoneme-specific gamma-augmentation ($p=0.01$ on Mann-Whitney U test).

Neurostimulation of 6 of the 10 left Rolandic sites showing phoneme-specific gamma-augmentation elicited sensorimotor symptoms involving the mouth, but failed to further sub-classify each of the six sites as the sensorimotor lip or tongue area in a clear-cut fashion. Neurostimulation of the remaining 4 left Rolandic sites failed to elicit a sensorimotor symptom involving the mouth or throat (Figure 4; Table S5 [supplementary data on the website]). On the other hand, neurostimulation of 4 of the 5 right Rolandic sites showing phoneme-specific gamma-augmentation elicited sensorimotor symptoms involving the throat; stimulation of the remaining one elicited movement of the mouth. The Fisher's Exact Probability Test for the 2×3 contingency table revealed that the left and right Rolandic sites showing phoneme-specific gamma-augmentation were frequently classified as the primary sensorimotor mouth and throat areas, respectively ($p=0.005$).

Conversely, time-frequency ECoG analysis relative to the onset of auditorily-presented syllables failed to demonstrate differential gamma-augmentation elicited by listening to a specific auditory-phoneme in the temporal neocortex in any subjects. Electrical neurostimulation of the temporal neocortex did not elicit perception of phoneme-like sounds in any subjects.

DISCUSSION

The major findings are summarized as follows. (i) Gamma-oscillations in the superior temporal gyrus were highly augmented during syllable-presentation, minimally augmented at the onset of syllable-articulation, and again highly augmented following syllable-articulation. (ii) Gamma-oscillations were augmented in the Rolandic area prior to and during syllable-articulation with the onset and peak occurring earlier in the left side. (iii) The sites showing large gamma-augmentation elicited by listening and overt repetition were generally concordant with clinical symptoms elicited by neurostimulation, as suggested by statistical analyses. (iv) Articulation of specific phonemes differentially augmented gamma-oscillations in subsets of inferior Rolandic sites more frequently in the left side. (iv) Such phoneme-specific differential gamma-augmentation in the left hemisphere was frequently noted in the primary sensorimotor *mouth* area, whereas such differential gamma-augmentation on the right was frequently noted in the sensorimotor *throat* area.

Significance of sequential gamma-modulation in the superior temporal gyrus

Our study demonstrated two temporally-separated peaks of gamma-augmentation elicited in the superior temporal gyrus; the first peak was associated with externally-presented syllables and the other associated with articulated syllables. This observation is consistent with a number of previous studies. Studies of humans and monkeys using ECoG demonstrated that auditory tones, vocal sounds and vocal words can elicit gamma-augmentation ranging from 40 to 160 Hz in the superior temporal gyrus in either hemisphere (Crone et al., 2001a; Brosch et al., 2002; Edwards et al., 2005; Bidet-Caulet et al., 2007; Brown et al., 2008; Ray et al., 2008b; Towle et al, 2008; Chandrasekaran and Ghazanfar, 2009). Studies of healthy adults using fMRI also localized overlapping regions for processing of both speech and non-speech sounds in the posterior-lateral portions of superior temporal gyri bilaterally (Belin et al., 2000; Binder et al., 2000; Jäncke et al., 2002; Warren et al., 2002; Joanisse and Gati, 2003; Callan et al., 2004; Burton and Small, 2006; Rimol et al., 2006; Lewis et al., 2009). It is likely that significance

of gamma-augmentation in the superior temporal gyrus seen in our study includes neural processing for auditory information at acoustic and/or phonetic levels.

Our observations derived from ECoG analyses *on each individual basis* were consistent with the previously-reported observations that gamma-augmentation in the superior temporal gyrus was transient and that the amplitude of gamma-oscillations returned to the baseline level immediately prior to the onset of articulation (Crone et al., 2001b; Towle et al, 2008). Taking into account the tight correlation between the power of gamma-oscillations on ECoG and the firing rate on single-unit recording (Ray et al., 2008a), a similar finding is expected to be observed in studies using single-unit recording. Indeed, previous studies of humans and monkeys using single-unit recording have demonstrated that neuronal responses to auditory-stimuli in a substantial proportion of auditory-cortex neurons are suppressed at the initiation of vocalization (Müller-Preuss and Ploog, 1981; Creutzfeldt et al., 1989; Eliades and Wang, 2003; 2005) but that a small subset of auditory-cortex neurons are rather sensitive to auditory feedback during vocal production (Eliades and Wang, 2008). Our ECoG analysis *on a group basis* (Figure 3A) revealed the presence of modest but statistically-significant gamma-augmentation in the superior temporal gyrus around the onset of syllable-articulation; further studies are needed to determine whether such modest gamma-augmentation represents increased feed-back or feed-forward activity for articulation.

Our study demonstrated that the magnitude and extent of gamma-augmentation elicited in the superior temporal gyrus were larger when vocal sounds were externally presented compared to when articulated; this observation is consistent with those reported in previous ECoG studies (Crone et al., 2001b; Towle et al, 2008). Plausible explanations for this observation include: (i) selective gating or inhibitory processes occurring for repeated auditory-syllables (Trautner et al., 2006), (ii) greater auditory processes occurring for strangers' vocal-sounds compared to articulated vocal-sounds, which are most familiar to each participant, (iii) greater encoding processes (Overath et al., 2008; Bonte et al., 2009) needed for externally-presented syllables, and (iv) the magnitude of auditory processing simply correlating to the volume of auditory stimuli.

Significance of gamma-modulation in the inferior Rolandic area

Did our study suggest that the inferior Rolandic area *primarily* contributes to speech perception? Previously proposed theories in cognitive neuroscience include the Motor Theory of Speech Perception (Liberman et al., 1967) that humans would perceive each spoken sound as each intended phonetic gesture. This theory has been at least partially supported by fMRI studies showing that motor circuits are activated when spoken phonemes are externally presented even without a speech-production task assigned to subjects (Wilson et al., 2004; Pulvermüller et al., 2006). Our study demonstrated that gamma-augmentation in the inferior Rolandic area was preceded by that in the superior temporal gyrus (Figure 3). Thus, our observation supports the opinion that the motor system is *not primarily* involved for speech perception (Lotto et al, 2009), although the inferior Rolandic area could *secondarily* modulate speech perception.

Which side of Rolandic area predominantly drives movement execution to overtly articulate phonemes in humans? A previous lesion study has shown that stroke involving the left Rolandic area was associated with more severe dysarthria compared to that involving the right (Woo et al., 1999). Previous fMRI studies showed that overt and covert speech production tasks elicited cortical activation involving both Rolandic areas with slightly larger extent in the left hemisphere (Pulvermüller et al., 2006; Dhanjal et al., 2008). Our study demonstrated that the onset and peak of cortical activation elicited by syllable-articulation occurred earlier in patients with ECoG sampled from the left hemisphere compared to the right. These observations support

the hypothesis that movement execution to articulate phonemes is predominantly driven by the primary sensorimotor area on the left side.

The novel observations in our study include that articulation of specific phonemes differentially elicited gamma-augmentation in subsets of the inferior Rolandic sites and that such phoneme-specific gamma-augmentation was observed more frequently in the left hemisphere compared to the right. Phoneme [f] is produced with the upper teeth placed on the lower lip, whereas phoneme [h] is produced with the upper and lower lips apart. Phoneme [i:] is produced with the lateral parts of the tongue contacting the hard palate, whereas phoneme [**ɑ**:] is produced with the tongue and the upper palate apart. Previous studies using neurostimulation demonstrated that the sensorimotor throat, tongue, lip, hand and leg areas are distributed from the bottom to the top of the Rolandic area (Penfield and Boldrey, 1937; Nii et al., 1996; Boling et al., 2002). A previous fMRI study showed that the primary somatosensory area for the lower-lip, side-lip, and upper lip are distributed in the Rolandic area from lower to upper direction (Huang and Sereno, 2007). Another fMRI study showed that covert articulation of phoneme [p] (requiring lip movement) activated the Rolandic site superior to that activated by phoneme [t] (requiring tongue movement); such cortical activation was more extensive in the left side (Pulvermüller et al., 2006). Taken together, we speculate that phoneme-specific differential gamma-augmentation in the Rolandic area is partially attributed to the mouth positioning during phoneme-articulation and that mouth positioning to articulate phonemes is executed and/or monitored predominantly by the primary sensorimotor *mouth* area on the left side.

Further studies are required to determine the significance of phoneme-specific differential gamma-augmentation in the primary sensorimotor *throat* area on the right side, and also to determine whether handedness or the side of language dominance has an effect on the spatial pattern of phoneme-specific differential gamma-activation. A previous imaging study showed that phonetic discrimination was associated with cortical activation in the left inferior frontal region, whereas pitch discrimination was associated with cortical activation in the right prefrontal area (Zatorre et al., 1992). In our study, however, subjects were not instructed to articulate syllables with a different pitch or volume.

Methodological issues

Studies using ECoG recording are inevitably associated with spatial sampling limitations. In our study, all subjects had subdural electrode coverage involving the lateral surface of superior temporal gyrus and Rolandic area. It is still uncertain whether the maximal cortical response was obtained from one of the active electrodes placed at every 1 cm distance, or the maximal response occurred from the brain region between subdural electrodes or the deeply-situated gyrus along a sulcus. Nevertheless, it should be emphasized that the number of sampling sites from the cortical areas of interest was reasonably balanced between the left and right hemispheres in our study. Thus, our observation that the onset and peak of gamma-augmentation occurred earlier in the left Rolandic area compared to the right cannot be simply attributed to the imbalanced number of sampling sites between hemispheres.

The present study failed to find a linear relationship between event-related gamma-augmentation and the age of subjects. It may be too premature to generalize our observations to a healthy population, since subjects in the present study consisted of patients with focal epilepsy. Potential confounding factors include antiepileptic drugs, underlying etiology, location of seizure foci, as well as distance between the seizure focus and the eloquent cortex. Multivariate analyses to exclude such confounding factors were not feasible, since only 15 subjects were included in the present study.

None of the subjects in the present study had a structural lesion in the posterior portion of superior temporal gyrus; nonetheless, it is still possible that failure to elicit an auditory

symptom using neurostimulation of the superior temporal gyrus was attributed to cortical dysfunction related to epilepsy or antiepileptic drugs. Since depth electrodes were not used in our study, the Heschl's gyrus (the medial portion of the superior temporal gyrus) was not sampled or stimulated in any of our subjects. Measurement of event-related gamma-oscillations is a study of cortical activation through tasks, whereas electrical neurostimulation often elicits a forced activation but at times may inhibit cortical function. Stimulation-induced activation but not inhibition of the primary auditory area would result in positive auditory percepts. These issues could explain why an auditory symptom failed to be elicited by neurostimulation in a substantial proportion of subjects in the present study.

ECoG recording from healthy humans is not tenable, and all of our subjects were patients with focal epilepsy. Thus, we cannot rule out the possibility that the effects of seizures and lesions have altered the magnitude of event-related gamma-oscillations. A previous study of rats showed that lesioning of the entorhinal cortex resulted in decreased physiological gamma-oscillations in the hippocampus (Bragin et al., 1995). In addition, possibility of reorganization of eloquent cortices cannot be ruled out. To increase the generalizability of our results, patients with massive brain malformations and those with subsequent surgical resection involving seizure onset arising from either the posterior superior temporal gyrus or inferior Rolandic area were excluded from our study. Although *localization* of eloquent cortices may have been altered by the underlying disease process in some of our subjects, it would be plausible to assume that the *sequential order* of eloquent areas participating in the speech process (i.e.: perception of externally-presented syllables, encoding of syllables, movement execution to articulate syllables, and perception of articulated syllables) would be similar between epileptic patients and healthy individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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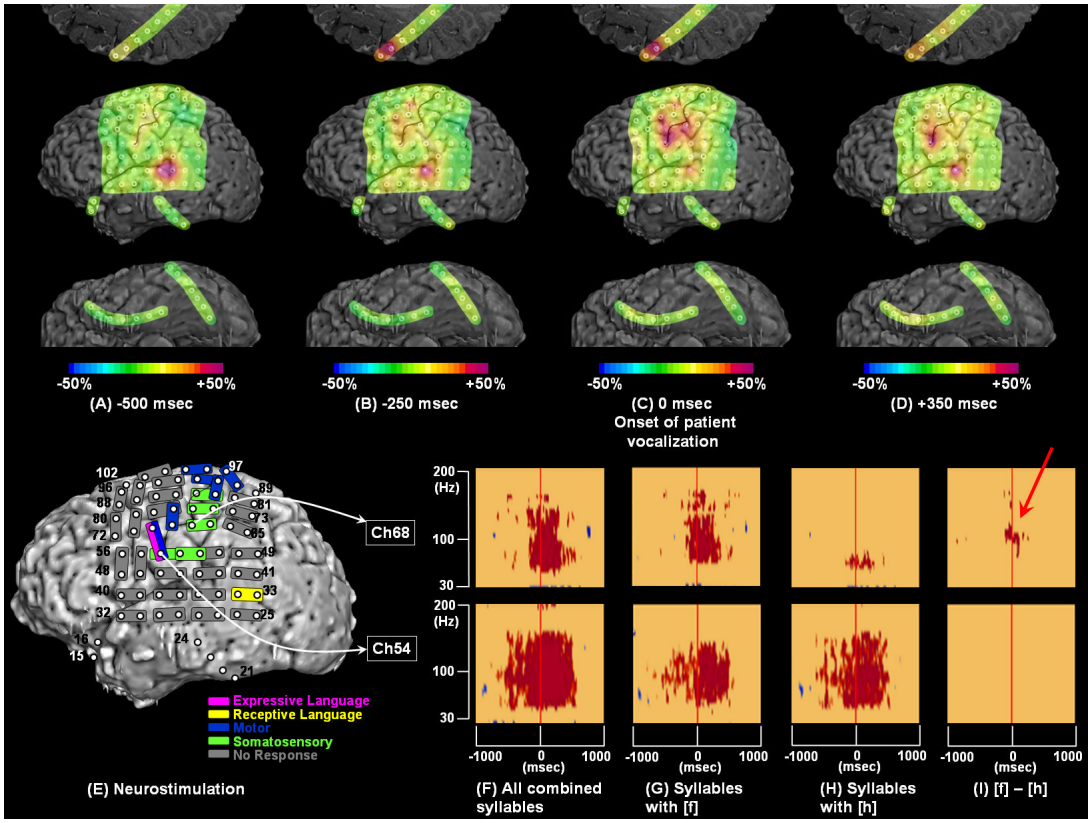

Figure 1. The results of time-frequency ECoG analysis and electrical neurostimulation in a 16-year-old right-handed boy with focal epilepsy (patient 4)

The results of time-frequency analysis of ECoG traces time-locked to the onset of syllable-articulation are shown. Cortical activation represented as increased 'gamma-range amplitude' (50 – 150 Hz) successively involved (A) the superior temporal gyrus 500 msec prior to the onset of syllable-articulation, (B) the medial superior frontal gyrus 250 msec prior to the onset of syllable-articulation, (C) the inferior pre- and post-central gyri at the onset of syllable-articulation and (D) the superior temporal gyrus following the onset of syllable-articulation. (E) Electrical neurostimulation of an electrode pair on the inferior Rolandic area (Ch53 & 54) elicited tingling of the mouth predominantly involving the tongue at 6 mA of stimulation. Stimulation of an electrode pair of the posterior frontal lobe (Ch54 & 70) elicited pure speech arrest at 6 mA of stimulation and speech arrest associated with mouth movement involving the tongue and lip at 9 mA of stimulation. Stimulation of an electrode pair on the inferior Rolandic area (Ch67 & 68) elicited tingling of the mouth involving the lip and tongue at 6 mA of stimulation. (F) Time-frequency analysis of ECoG traces relative to the onset of articulation demonstrated that articulation of all combined syllables elicited significant gamma-augmentation (denoted by red voxels) involving 50 – 150 Hz at Ch 54 and Ch 68 around the onset of articulation. (G) Similarly, articulation of syllables containing phoneme [f] elicited significant gamma-augmentation at Ch 54 and Ch 68. (H) Articulation of syllables containing phoneme [h] elicited gamma-augmentation at Ch 54 to a similar extent but less intensely at Ch 68. (I) Ch 68 (see red arrow) but not Ch 54 revealed differential gamma-augmentation elicited by articulation of phoneme [f] more than phoneme [h].

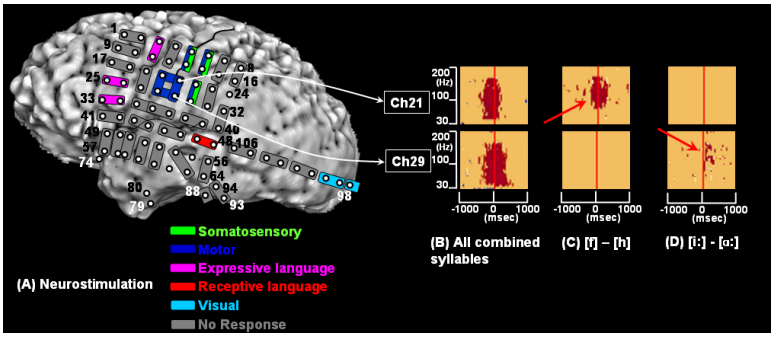

Figure 2. The results of time-frequency ECoG analysis and electrical neurostimulation in a 17-year-old right-handed boy with focal epilepsy (patient 6)

(A) Electrical neurostimulation of an electrode pair on the inferior Rolandic area (Ch20 & 21) elicited movement of the mouth predominantly involving the lip at 3 mA of stimulation. Stimulation of an electrode pair (Ch28 & 29) elicited movement of the mouth predominantly involving the tongue at 3 mA of stimulation. Stimulation of an electrode pair (Ch21 & 29) elicited movement of the mouth involving both tongue and lip at 3 mA of stimulation. (B) Time-frequency analysis of ECoG traces relative to the onset of articulation demonstrated that articulation of all combined syllables elicited significant gamma-augmentation (denoted by red voxels) involving 50 – 150 Hz at Ch 21 and Ch 29 around the onset of articulation. (C) Differential gamma-augmentation elicited by articulation of phoneme [f] more than phoneme [h] was noted at Ch 21 located superior to Ch 29. (D) Differential gamma-augmentation elicited by articulation of phoneme [i:] more than phoneme [**ɑ**:] was noted at Ch 29 located inferior to Ch 21.

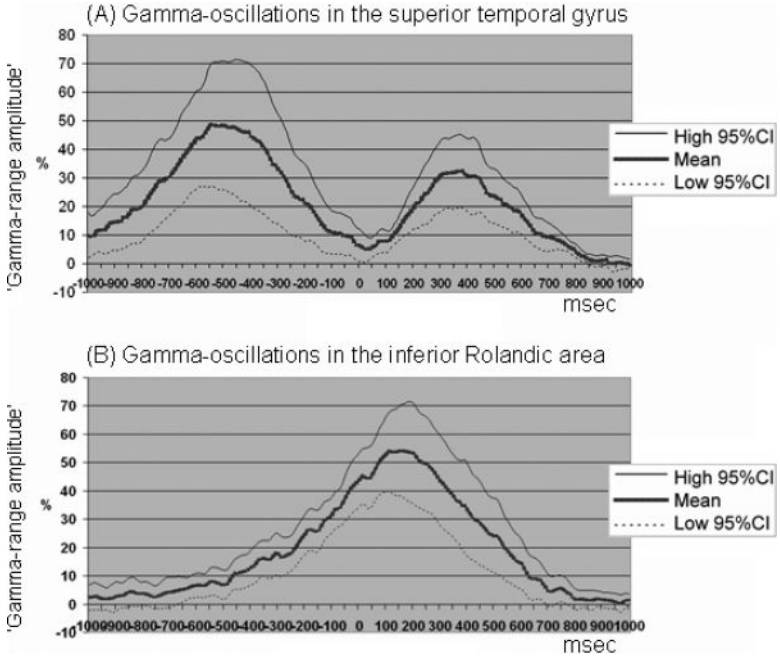

Figure 3. Sequential changes of 'gamma-range amplitude' in the superior temporal gyrus and inferior Rolandic area

(A) Using ECoG traces relative to the onset of syllable-articulation, the sequential change of 'gamma-range amplitude' in '*the center of syllable-related gamma-oscillations*' within the superior temporal gyrus is shown. Group analysis suggested that the mean 'gamma-range amplitude' ranged 40 - 50% at -630 to -350 msec, decreased as low as 5 - 10% at −50 to +120 msec, and increased up to 30 - 33% at +300 to +430 msec relative to the onset of syllable-articulation. (B) The sequential change of 'gamma-range amplitude' in 'the center of articulation-related gamma-oscillations' within the inferior Rolandic area is similarly shown. Group analysis suggested that the mean 'gamma-range amplitude' ranged below 10% before −460 msec relative to the onset of syllable-articulation, increased up to 40 - 55% at −30 to +330 msec, and decreased below 10% at +630 msec and after. 95%CI: 95% confidence interval.

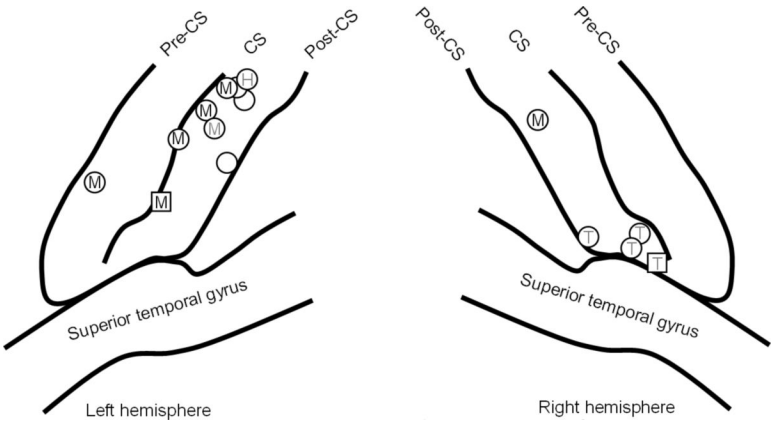

Figure 4. Differential gamma-augmentation elicited by articulation of specific phonemes

Ten sites in the left Rolandic area and five in the right Rolandic area showed differential gamma-augmentation elicited by articulation of a specific phoneme. Each circle represents the electrode site showing differential gamma-augmentation more intensely elicited by articulation of phoneme [f] than that of phoneme [h], whereas each square represents that more intensely elicited by articulation of phoneme [i:] than that of phoneme [**ɑ**:]. M (black): Neurostimulation elicited a motor symptom involving the mouth. M (gray): a somatosensory symptom involving the mouth. H (gray): a somatosensory symptom involving the hand. T (gray): a somatosensory symptom involving the throat. Neurostimulation of the remaining three sites in the left side failed to elicit clinical symptoms. CS: central sulcus. Pre-CS: pre-central sulcus. Post-CS: post-central sulcus.