# Rapid and Minimum Invasive Functional Brain Mapping by Real-Time Visualization of High Gamma Activity During Awake Craniotomy

*Hiroshi Ogawa[1], Kyousuke Kamada[1], Christoph Kapeller[2], Satoru Hiroshima[1], Robert Prueckl[2], Christoph Guger[2]*

**Key words**
- Awake craniotomy
- Electrocorticogram
- High gamma activity
- Real-time mapping

**Abbreviations and Acronyms**
**AM**: Ankle movement
**BOLD**: Blood oxygenation-level dependent
**ECoG**: Electrocorticogram
**ECS**: Electrocortical stimulation
**fMRI**: Functional magnetic resonance imaging
**FT**: Finger tapping
**HGA**: High gamma activity
**IFG**: Inferior frontal gyri
**MRI**: Magnetic resonance imaging
**PN**: Picture naming
**WR**: Word reading

*From the [1]Department of Neurosurgery, School of Medicine, Asahikawa Medical University, Asahikawa, Japan; and [2]Guger Technologies OG, Graz, Austria*

*To whom correspondence should be addressed: Kyousuke Kamada M.D., Ph.D. [E-mail: kamady-k@umin.ac.jp]*

*Citation: World Neurosurg. (2014) 82, 5:912.e1-912.e10. http://dx.doi.org/10.1016/j.wneu.2014.08.009*

*Journal homepage: www.WORLDNEUROSURGERY.org*

*Available online: www.sciencedirect.com*



BACKGROUND: **Electrocortical stimulation (ECS) is the gold standard for functional brain mapping during an awake craniotomy. The critical issue is to set aside enough time to identify eloquent cortices by ECS. High gamma activity (HGA) ranging between 80 and 120 Hz on electrocorticogram is assumed to reflect localized cortical processing. In this report, we used real-time HGA mapping and functional neuronavigation integrated with functional magnetic resonance imaging (fMRI) for rapid and reliable identification of motor and language functions.**

METHODS: **Four patients with intra-axial tumors in their dominant hemisphere underwent preoperative fMRI and lesion resection with an awake craniotomy. All patients showed significant fMRI activation evoked by motor and language tasks. During the craniotomy, we recorded electrocorticogram activity by placing subdural grids directly on the exposed brain surface.**

RESULTS: **Each patient performed motor and language tasks and demonstrated real-time HGA dynamics in hand motor areas and parts of the inferior frontal gyrus. Sensitivity and specificity of HGA mapping were 100% compared with ECS mapping in the frontal lobe, which suggested HGA mapping precisely indicated eloquent cortices. We found different HGA dynamics of language tasks in frontal and temporal regions. Specificities of the motor and language-fMRI did not reach 85%. The results of HGA mapping was mostly consistent with those of ECS mapping, although fMRI tended to overestimate functional areas.**

CONCLUSIONS: **This novel technique enables rapid and accurate identification of motor and frontal language areas. Furthermore, real-time HGA mapping sheds light on underlying physiological mechanisms related to human brain functions.**

## INTRODUCTION

Language functions are generated through complex neural networks (4). To improve our understanding of language mechanisms, it is necessary to construct detailed brain maps via the use of functional imaging and electrophysiological techniques (12, 20, 38). However, maximal resection of brain tumors from eloquent areas carries a high risk of neurologic consequences for higher brain functions, including fine motor and language functions (16). It is, therefore, indispensable to identify and protect the eloquent cortices from surgical injury.

Several groups have proposed that electrocortical stimulation (ECS) during awake craniotomy is a reliable way to perform brain mapping (8, 33, 37); however, technical issues for this method still remain, such as extended operation time to search eloquent areas by stimulating multiple points with various stimulus intensities and seizures risks for functional mapping. Therefore, it is desirable to rapidly and accurately identify the eloquent areas within the restricted time available during an awake craniotomy.

There are 2 practical and less-invasive techniques than ECS that can visualize a given brain region and identify its functions both before and during operation. One is preoperative imaging of blood oxygenation level–dependent (BOLD) responses, which has been known as functional magnetic resonance imaging (fMRI) in the past 2 decades (2, 11, 12, 28). Higher-order cognitive functions such as language seem to have wider activation areas on fMRI than what can be revealed with ECS mapping (20, 32, 34). To reliably use fMRI in the clinical setting, we must clarify the situations in which the BOLD signal accurately portrays neural activity when using higher magnetic field systems, multi-channel coils, or other new sequences (1, 10, 13, 15, 18, 26, 42).

Power changes in oscillatory neuronal activity within various frequency ranges revealed with electrocorticogram (ECoG) recently have received attention as a potential physiological correlate of BOLD responses (5, 15, 17). Among these oscillatory changes, the augmentation of high gamma activity (HGA) ranging approximately

80–120 Hz is assumed to reflect localized cortical processing (39) and has been correlated with BOLD responses mainly in the primary visual, auditory, and motor cortices of humans. The assumption that HGA is a neural correlate of BOLD, i.e., HGA-BOLD coupling, is supported by the findings of several studies (5, 21, 27, 35). Approximately 74% of the brain's energy budget is estimated to be devoted to postsynaptic potentials (1). Crone et al. (7) constructed HGA maps that indicated language-related functions from patients performing word reading (WR) tasks. Therefore, it is anticipated that HGA should provide another key signal for accurate brain mapping.

On the basis these facts, we expected that HGA mapping becomes a new technique that minimizes a patient's stress and possibly shortens the operation time during an awake craniotomy. In this study, we propose the novel technique of real-time HGA mapping and fMRI-based functional neuronavigation during an awake craniotomy and demonstrate the clinical impact of this novel method in our representative experiences.

## MATERIALS AND METHODS

### Patients

Four patients with an intra-axial tumor affecting the frontotemporal motor and language areas of the dominant hemisphere underwent lesion resection with an awake craniotomy. The patients' demographic data are presented in **Table 1** and **Figure 1**. The patients underwent fMRI to identify the language and hand motor regions with functional mapping before operation. This study was approved by the institutional review board, and written informed consent was obtained from each patient before participating in the study.

### Technique

***Magnetic Resonance (MR) Protocols.*** All MR studies were performed preoperatively with a 3.0-T whole-body MR scanner with echo-planar capabilities and a 32-channel surface coil (Discovery 750W; General Electric, Milwaukee, Wisconsin, USA). Foam cushions were used during the experiments to immobilize the head.

Three-dimensional T1-weighted magnetic resonance imaging (MRI) of the brain were obtained for each patient, which consisted of 136 sequential, 1.4-mm-thick axial slices with a resolution of 256 × 256 pixels and field of view of 240 mm. We performed fMRI with a T2-weighted echo-planar imaging sequence (echo time, 62 ms; repetition time, 114 ms; flip angle, 80°; slice thickness, 3 mm with no gap; field of view, 240 mm; matrix, 128 × 128; 35 slices). Each fMRI session consisted of 3 dummy scan volumes, 3 activation periods, and 4 baseline (rest) periods, resulting in 2 minutes, 32 seconds. During each period, 5 echo-planer imaging volumes were collected by delivering triggers to a stimulus computer, which yielded 38 imaging volumes. We used g.USBamp with a visual stimulation program (g.tec; Guger Technologies OG, Graz, Austria) to present visual stimuli to the patients that were synchronized with the fMRI via hardware triggers.

***fMRI Tasks.*** *WR Task.* Visual stimuli were presented to the patients with a liquid crystal display monitor that reflected onto a mirror positioned above the head coil. During the active periods, words consisting of 3 Japanese letters were presented for 2000 milliseconds and interleaved between 500-millisecond interstimulus intervals. The patients were instructed to silently categorize the presented word as either "abstract" or "concrete," based on the nature of the word. During the rest periods, the patients passively viewed dot clusters that were presented and with the same luminance as the stimuli to eliminate primary visual responses.

*Picture Naming (PN) Task.* In the same setting as the WR task, patients were instructed to silently name the objects presented in color illustrations. The illustrations were presented for 2000 milliseconds and interleaved between 500-millisecond interstimulus intervals. During the rest periods, the patients passively viewed destructured pictures that were presented with the same luminance as the stimuli shown in the active periods.

*Finger Tapping (FT) Task.* During the active period of the FT task, patients were asked to perform FT in response to auditory pacing cues. During the rest period, patients concentrated on their heart beat without movement.

***MR Postprocessing and Analysis.*** For the postdata acquisition analysis, we used Dr. View (Asahi Kasei, Tokyo, Japan). After MR data acquisition, the images were realigned with a 3-dimensional motion correction program and spatially smoothed using a Gaussian filter (8-mm kernel). Preprocessed data for each patient were analyzed with the standard general linear model approach using boxcar predictors convolved with the canonical hemodynamic response function. Pixels with a Z-score greater than 2.2 were considered to indicate fMRI activation. For each patient, the fMRI results were co-registered and fused with the corresponding 3-dimensional MRI of the patient's head with the affine transformation, thus maximizing the mutual information between the data sets. The fused images were transferred to our neuronavigation system and reconstructed in 3D to visualize the anatomy, lesioned site, and distributions of cortical functions.

**Table 1.** Demographic Patient Data

| Case No. | Age, years, Sex | Dominant Hemisphere | Tumor Location | Symptoms | Pathologic Diagnosis |
|---|---|---|---|---|---|
| 1 | 49, Male | Left | Left front-temporal lobe | Dysarthria | Glioblastoma |
| 2 | 41, Male | Left | Left parietal lobe | Dysarthria | Glioblastoma |
| 3 | 65, Male | Left | Left frontal lobe | Mild right hemiparesis | Anaplastic astrocytoma |
| 4 | 61, Male | Left | Left frontal lobe | Dysarthria | Glioblastoma |

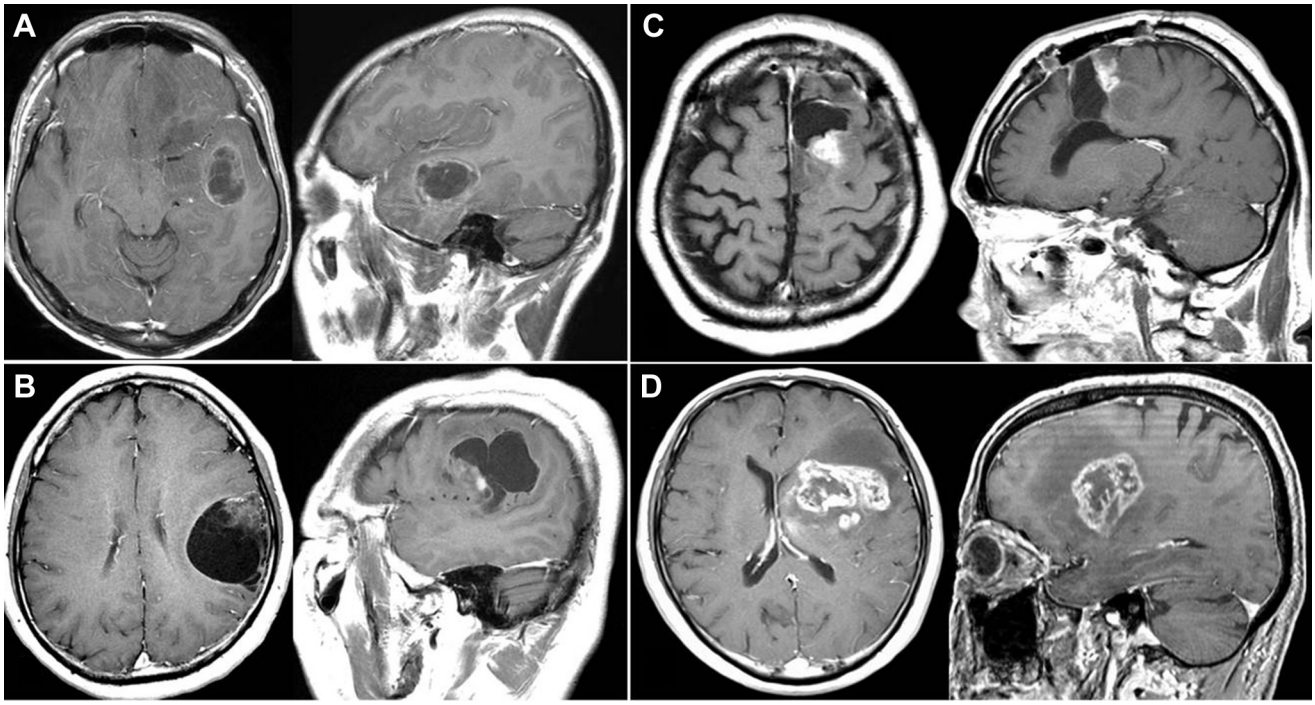


**Figure 1.** (**A**) Preoperative contrast-enhanced, T1-weighted magnetic resonance imaging (MRI) of case 1 showing a lesion with ring-like enhancement in left temporal lobe and a hypointense tumor in the left frontal lobe with a mass effect. (**B**) Preoperative contrast-enhanced, T1-weighted MRI of case 2 demonstrating a heterogeneous intensity nodule with a cystic component in the left frontoparietal region. (**C**) Contrast-enhanced, T1-weighted MRI of case 3 revealed heterogeneous tumor recurrence adjacent to the resection cavity (**D**) Preoperative contrast-enhanced, T1-weighted MRI of case 4 indicating heterogeneous enhancement lesion with edema in the left frontal lobe.

***Intraoperative ECoG Recording.*** All patients underwent an ECoG recording before the lesion resection and during an awake craniotomy. We used two 20-channel ECoG grids and 4-channel strip electrodes constructed from silicon sheets embedded with 3-mm diameter platinum electrodes that were spaced with a 10-mm interelectrode distance (Unique Medical, Tokyo, Japan). Only in case 4, we tried to use a 60-channel grid. The electrodes were 2 mm in diameter with 5-mm interelectrode spacing (Unique Medical, Tokyo, Japan). The electrodes were positioned on the exposed brain and were registered by the neuronavigation system. The electrode placement was recorded with photographs taken before the tumor resection. One channel of the strip electrode was used as a reference and the other as a ground. The ECoG data were recorded digitally with a 1200-Hz sampling rate and using a 256-channel g.HIamp biosignal amplifier. ECoG data were recorded with a 24-bit resolution and a high oversampling to increase the signal-to-noise ratio (g.tec; Guger Technologies OG).

For the intraoperative ECoG recordings, each patient was first asked to be relaxed for 20 seconds during the rest period (baseline) and then perform the FT task as it was performed for the fMRI task by tapping their finger for 20 seconds (active phase). The baseline and active phase were performed 3 times in this order, for a total of 2 minutes. Patients then performed the same language tasks they performed during fMRI scanning. A portable monitor was connected to the stimulus computer and was placed 30 cm in front of the patient. Visual stimuli were presented on the monitor using a real-time processing system driven by the g.HIamp, For the WR task, the patient read aloud Japanese words that were presented for 2000 millliseconds and interleaved between 500-millisecond interstimulus intervals. ECoG measurements were repeated during the WR task to confirm their reproducibility. In the WR task, the color pictures were presented with the same settings used for the fMRI task. In the PN task, the patients overtly named the objects. To obtain the baseline ECoG, the patients passively viewed destructured pictures that were presented with the same luminance as the stimuli presented in the active phases.

***ECoG Data Analysis.*** The ECoG data were performed using cortiQ (29) in MATLAB R2012a (Mathworks; Natick, Massachusetts, USA), which ran on the data acquisition computer that acquired data from the g.HIamp via USB. After channels containing singular noise and epileptic activity were excluded, we performed a common average reference to suppress common mode signals and calculated the baseline ECoG activity of each channel in the gamma frequency range 80—120 Hz. The patient was then instructed to perform a specific task, and the program was analyzing the ECoG activity during the task. To obtain power averages across HGA, we standardized the power spectral density values with respect to 20 s × 3 ECoG data epochs that

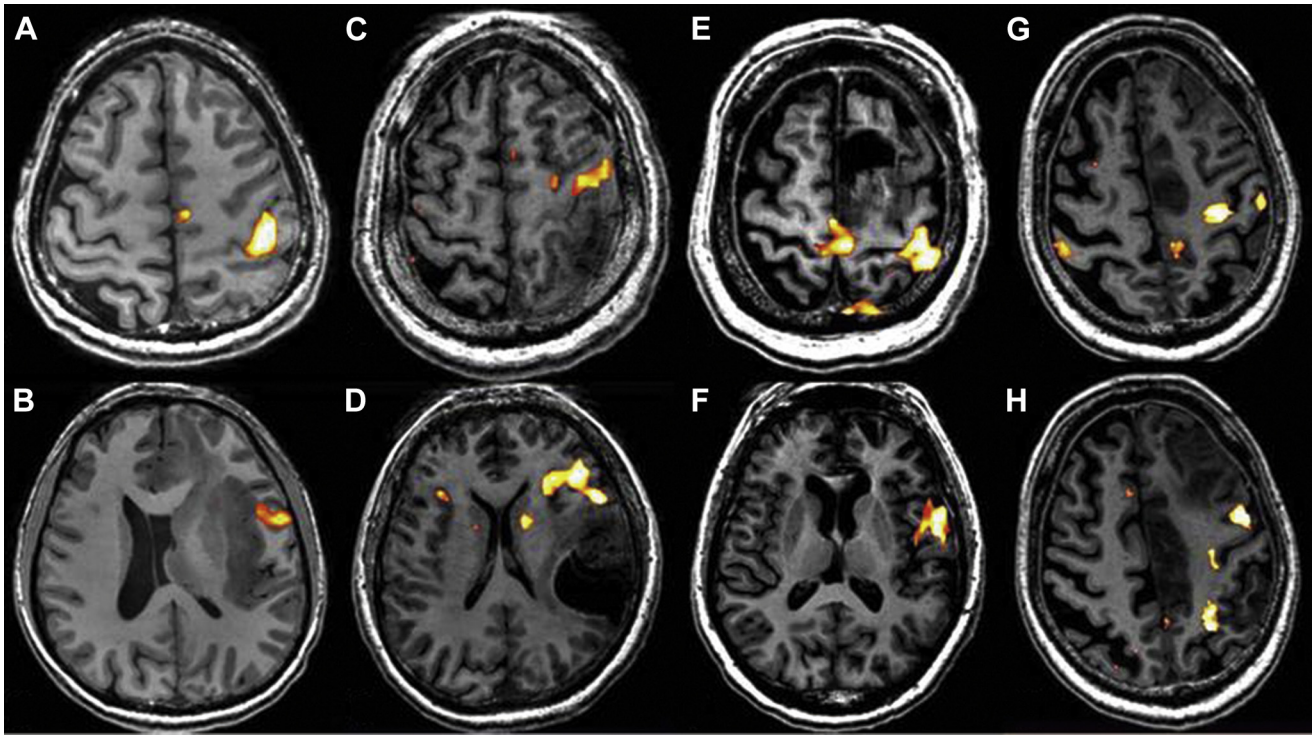


**Figure 2.** (**A** and **B**) Functional magnetic resonance imaging (fMRI) by finger tapping (FT) and word reading (WR) tasks of case 1 showing task-related activations in the primary hand-motor cortex and inferior frontal gyrus, respectively. (**C**) fMRI by FT task of case 2 demonstrating small activation in the motor cortex, which was compressed by the tumor. (**D**) fMRI by WR task of case 2 revealing obvious language-related activation in the frontal lobe. (**E**) fMRI by FT task of case 3 showing wide-spread motor-related activations. (**F**) fMRI by WR task of case 3 delineating the frontal language activations. (**G**) fMRI by FT task of case 4, showing activation as well as the other cases. (**H**) fMRI by WR task of case 4, indicating language-related activation in the frontal lobe.

included baseline and active phases. A t-test was used to determine whether HGA values in the active phases were significantly different from those in the baseline; $P$ values $< 0.05$ were considered statistically significant after Bonferroni correction. The analyzed result of each task appeared in real time on the MATLAB environment as red circles overlaying the electrodes, depending on the statistic significance. The significance value was represented by the circle's diameter. The computations were performed in realtime and updated at 20 Hz.

***ECS Mapping.*** After the ECoG recording, a biphasic electrical pulse (frequency, 50 Hz; pulse duration, 1 ms) was applied to the brain of awake patients using a bipolar electrode with a distance of 6 mm between tips (Ojemann Cortical Stimulator; Unique Medical, Tokyo, Japan). Cortical mapping was performed after the tumor and sulci/gyri were identified with the functional neuronavigation. Motor mapping was performed first to determine the appropriate stimulus intensity at the primary hand-motor cortex. The stimulus intensity was determined for each patient by first applying the stimulation at 3 mA and progressively increasing the current until the stimulation evoked a muscle twitch. The stimulation current was increased up to 10 mA to avoid triggering seizures. Once the threshold was determined with motor mapping, the same stimulus current was used for language mapping. We systematically used simple language tasks, which included spontaneous speech, WR, and PN, as we applied ECS. The stimulus sites were registered by the functional neuronavigation system. The patient was first asked to repeatedly speak a sentence "Today, the weather is good." For the WR and PN tasks, we presented 20 different words or pictures to the patient and marked the cortical regions, where ECS produced speech arrest or difficulty with naming objects (i.e., anomia). The stimulation sites were marked with sterilized tags.

## RESULTS

### Patient Symptoms and Task Performance

Although the third patient had mild hemiparesis, all 4 patients showed little impairment of language functions. They practiced the motor and language tasks before the operation and could read words and name pictures without difficulty. We confirmed a greater than 90% performance rate in each task for each patient. fMRI during the FT task clearly indicated increased activity in the hand motor representation in 3 cases (Figure 2). Case 3, who had a mild right hemiparesis, showed widespread fMRI activation over the motor and

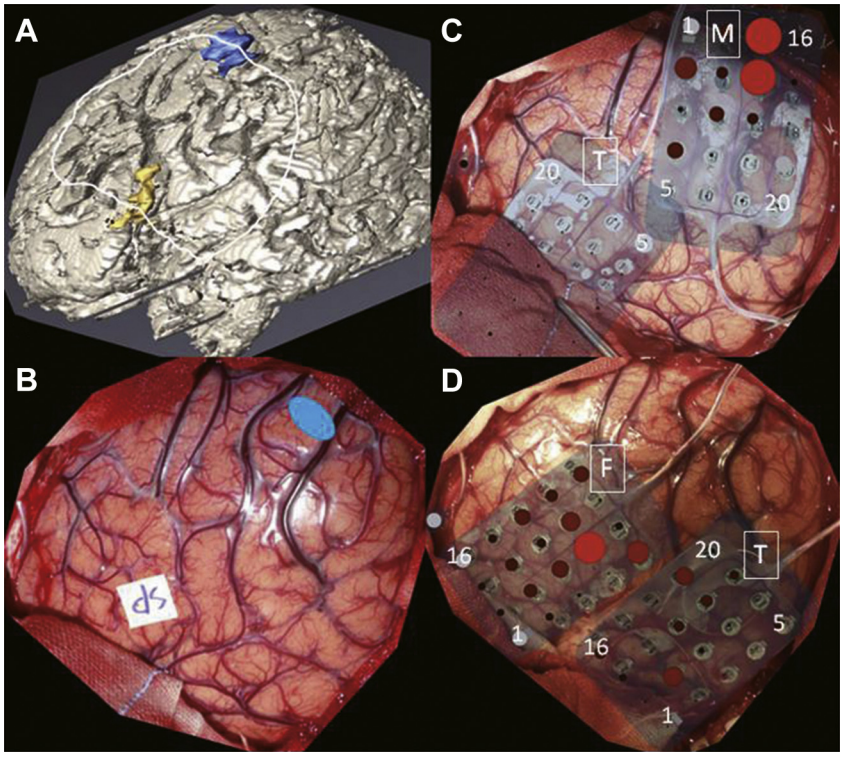


**Figure 3.** Functional localization for patient 1. (**A**) Three-dimensional reconstructed magnetic resonance imaging (MRI) including functional MRI (fMRI) activations showing craniotomy (*white circle*), finger-tapping (FT) fMRI activations (*blue*), and WR-fMRI activations (*yellow*). Note that craniotomy exposed the primary motor and frontal language areas. (**B**) Results of electrocortical stimulation validating the primary hand-motor cortex (*blue*) and frontal language area (a tag of "SP"). (**C**) Real-time high gamma activity (HGA) mapping by FT task showing significant HGA increase (*red circles* of M11 and 12) in the primary motor cortex. (**D**) Real-time HGA mapping by WR task showing significant HGA increase (a *red circle* of F9) in the inferior frontal gyrus.

somatosensory cortices (Figure 2E). During the WR and PN tasks, fMRI in all cases revealed a clear language lateralization and activated pixel clusters mainly in the frontal lobe, including the inferior (IFG) and middle frontal gyri, the dorsolateral prefrontal cortex. Activity in IFG and middle frontal gyri was significantly lateralized, indicating the dominant hemisphere. For all patients, the temporal and parietal lobes were less active than the frontal lobe while performing language tasks (Figure 2B, D, and F). On the basis of the fMRI results, we were confident that the patients would be able to perform the tasks during awake craniotomy.

## Intraoperative ECoG Recording

After performing the craniotomy, we confirmed the patient was awake and could easily follow verbal commands and answer simple questions. We identified the brain lesion and anatomical structures by visually inspecting the brain and using the functional neuronavigation. In the case 1, 2, and 4, we positioned the subdural grids directly on the exposed brain over the areas of interest, which depended on the task. Because the third patient was undergoing a third resection as the result of tumor recurrence, the dura mater adhered tightly to the cortex and restricted electrode positioning. Therefore, we slipped a strip electrode between the falx and mesial frontal cortex and inserted a strip electrode and a grid under the dura matter, thereby covering the exposed brain area and hidden frontal pole.

***Case 1.*** The first patient repeated all tasks to show their reproducibility. The FT-ECoG recorded a significant HGA increase in 2 channels that corresponded to the hand motor area (FT-HGA). In contrast, WR-ECoG revealed only one active channel that corresponded to the IFG (WR-HGA), but no HGA increase in other frontal regions. An increased HGA on the PN-ECoG (PN-HGA) was observed on the same electrode of the WR-HGA (Figure 3). ECS applied at 5 mA to the FT-HGA area (channels M11 and M12, Figure 3C) evoked a muscle contraction in the right hand and a partial seizure that persisted for several minutes. After FT-HGA mapping, ECS applied to the WR- and PN-HGA areas (channel F9, Figure 3D) consistently evoked speech arrest or naming difficulty. The sensitivity and specificity of FT-, PN-, and WR-HGA mapping were 100% and 100% compared with ECS mapping, respectively. Although sensitivities of FT- and all language-fMRI were 100%, specificities of FT-fMRI and language-fMRI were 81.6% and 80.6%, respectively. Language-fMRI activations were larger, but involved WR- and PN-HGA areas. Real-time HGA mapping matched the ECS results perfectly and predicted the eloquent areas.

In the ECoG analysis, we observed significant differences in the "HGA dynamics" among FT, WR, and PN in all patients. Although FT-HGA appeared consistently only on 2 electrodes, WR-HGA was visible approximately 10 seconds into the first active period for channels T9, T13, T14, and T15 (Figure 4A) of the superior temporal gyrus but immediately diminished. The frontal region showed longer WR-HGA activation on channels F5, F9, and F11 (Figure 4A), despite a short duration of HGA activation for the temporal lobe. We found similar results in the PN-HGA analysis, which demonstrated the long-term WR-HGA persisted only in channel F9 (Figure 4B) of the frontal lobe; this finding was in contrast to the short activation observed for the superior and middle temporal lobes. After tumor resection, the patient suffered from transient motor-dominant aphasia for a week.

***Case 2.*** In patient 2, 2 electrodes (channels M11 and M16, Figure 5A) of FT-HGA clearly indicated the hand motor area. WR-HGA appeared in 4 channels (channels F4, F5, F14, and F15, Figure 5B) on IFG, suggesting that the exposed cortex that included the tumor did not mediate language functions. ECS applied to the

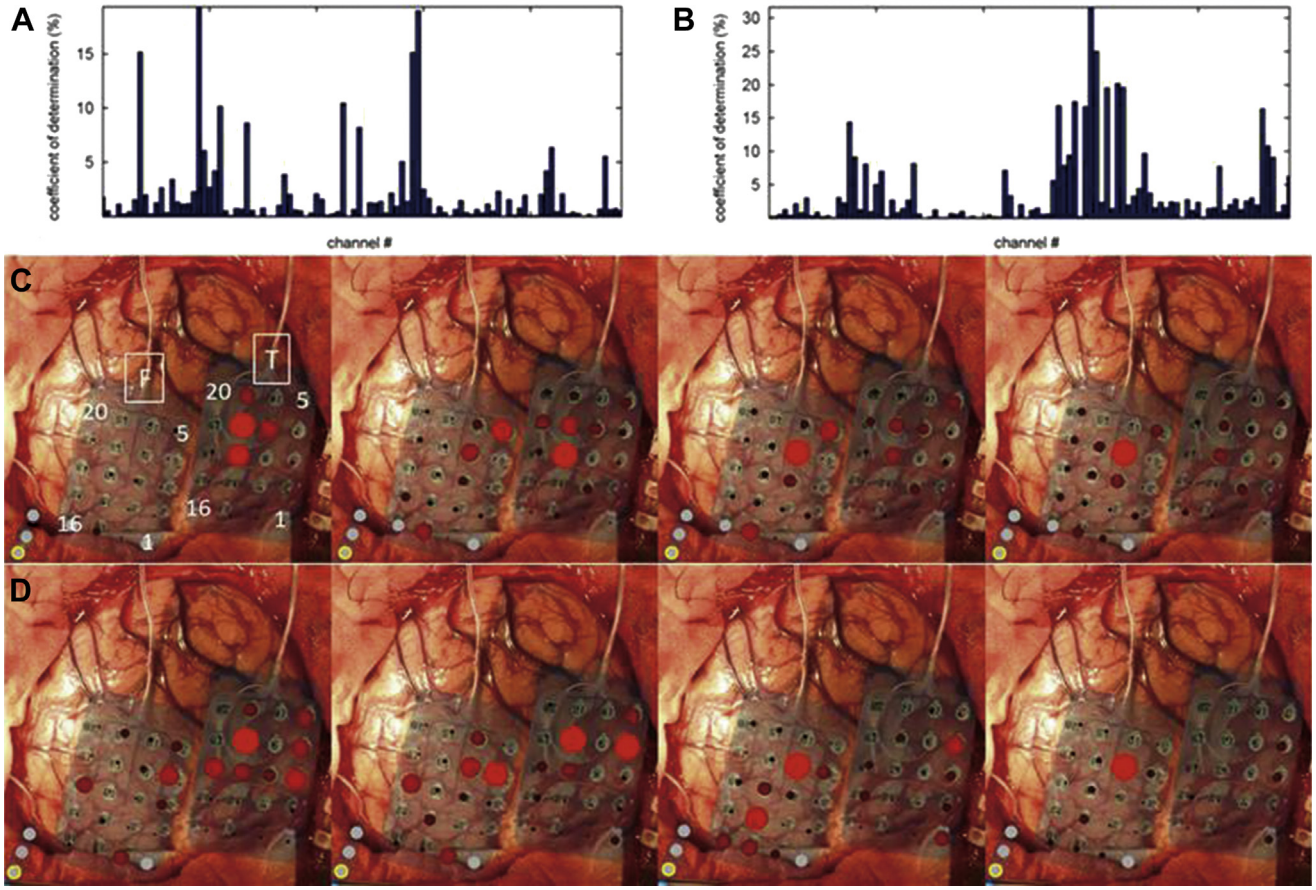


**Figure 4.** High gamma activity (HGA) power spectra graph (**A, B**) and HGA dynamics (**C, D**) for patient 1. The graph of word reading (WR) task (**A**) and hand grasping task (**B**) were obtained during real-time HGA mapping. HGA dynamics related to WR (**C**) and picture naming (PN) (**D**) tasks are shown below the graph. Each frame shows HGA profiles at 5, 10, 15, and 20 seconds, respectively. Note transient HGA appeared in the initial frames on the temporal lobe. The frontal HGA (a *red circle* of F9) remained at 20 seconds after the task initiation.

localized FT-HGA area initially showed hand muscle contractions but subsequently caused a generalized seizure. We skipped further ECS mapping because the stimulation frequently induced seizures.

FT- and language-fMRI results were validated by ECS, FT-HGA, and language-HGA (Figure 5). Sensitivity and specificity of FT-HGA mapping were 100% and 100% compared with ECS mapping, respectively. By contrast, those of FT-fMRI were 100% and 76.3%, which indicated fMRI activation was much wider in extent. Because we interrupted ECS as a result of the seizure, we used HGA mapping as reference for further comparison. Sensitivity and specificity of language-fMRI were 100% and 84.2%, respectively.

WR-fMRI activation appeared wider than WR-HGA. The WR-HGA dynamics demonstrated long-term WR-HGA only in channels F4, F5, F14, and F15 (Figure 5D) on the frontal lobe. This finding was in contrast to the short-term HGA observed in several channels on the perisylvian region. After surgery, the patient had no deterioration of the motor and language-related functions.

***Case 3.*** Patient 3 suffered from frequent focal seizures and mild hemiparesis as the result of several operations that were performed for tumor recurrence. FT-HGA was apparent in more than 6 channels that covered the hand motor area, the somatosensory cortex, and the surrounding regions under the dura matter. The wide FT-fMRI activations around the hand-motor area were similar with FT-HGA in size (Figure 6A and 6B). One channel of the inserted strip electrode (channel HM 1, Figure 6C) showed increased HGA that corresponded with ankle movement (AM) on the mesial surface of the frontal gyrus, which was minimally exposed because of the dural adhesion and venous structures. AM-HGA also appeared over other motor cortex regions (channels M18 and M19, Figure 6C). WR- and PN-fMRI demonstrated the activation mainly in the left IFG, which was much far from the lesion.PN and WR elicited little HGA activation other than the mouth motor area (channel M2, Figure 6D) because the electrodes did not reach the frontal language area. We skipped ECS in this patient because he frequently suffered from seizures and used HGA mapping as a reference for the comparison of fMRI. Sensitivity and specificity of FT-fMRI were

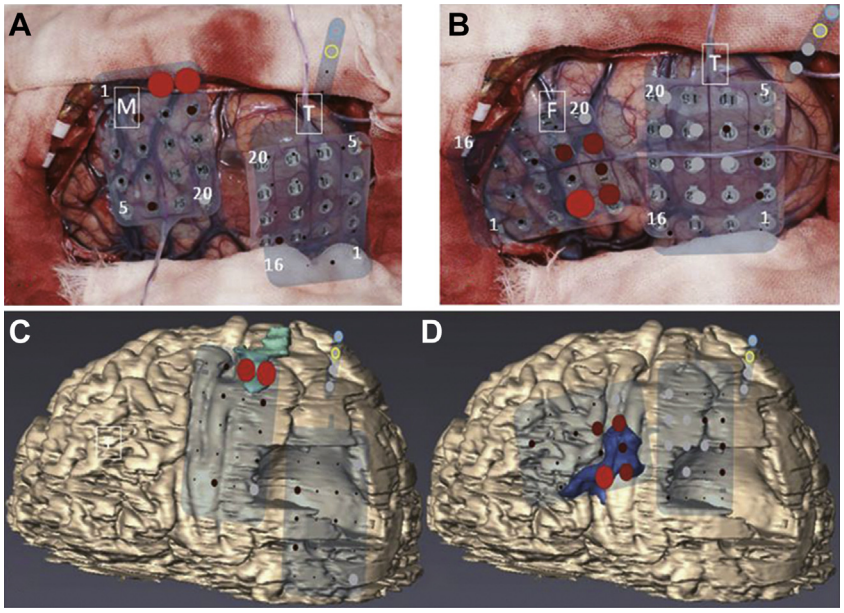


**Figure 5.** Functional localization for patient 2. (**A**) Real-time high gamma activity (HGA) mapping by finger-tapping (FT) task showing significant HGA increase (*red circles* of M11 and 16) in the primary motor cortex. (**B**) Real-time HGA mapping by word reading (WR) task showing significant HGA increase (*red circles* of F4, 5, 14, 15) in the inferior frontal gyrus. (**C** and **D**) 3-dimensional reconstructed magnetic resonance imaging (MRI) showing FT- and WR-HGA mainly appeared in FT- and WR-functional MRI activations, respectively.

100% and 70%, whereas those of AM-fMRI were 100% and 71.4%, respectively. We resected the lesion on the basis of real-time HGA mapping and the neurologic symptoms. His postoperative condition was uneventful, except a transient weakness of the right lower extremity.

***Case 4.*** Although patient 4 had mild motor dominant aphasia, he achieved the motor semantic tasks. Real-time HGA mapping indicated the temporal and frontal language centers. On the basis of ECS mapping, we confirmed that electrodes with increased HGA indicated the hand-motor and frontal language areas (**Figure 7**). After surgery, the patient had no deterioration of the motor and language-related functions.

Postoperative MRI demonstrated total removal of the enhancing lesion in all the cases. Real-time HGA mapping precisely revealed functional distributions in all patients for both the exposed cortex and the hidden regions owing to dura matter adhesion.

Although number of patients was 4, case 3 had no ECS mapping. We therefore calculated investigation times of HGA and ECS mapping in cases 1, 2, and 4. As a result, the investigation time was $9.3 \pm 2.3$ minutes for HGA mapping and $26.3 \pm 8.0$ minutes for ECS mapping ($P = 0.046 < 0.05$). There were significant differences between the 2 procedures.

## DISCUSSION

We have demonstrated a novel technique that uses real-time HGA mapping during awake craniotomies. Combining HGA mapping with fMRI-based functional neuronavigation enabled rapid identification of functional centers with high reliability, for language and motor functions. This procedure has the following advantages: Preoperative fMRI noninvasively suggests eloquent cortices. Real-time HGA mapping facilitates significant shortening of functional mapping and detecting functional representations of hidden cortical regions by dura mater. Preoperative fMRI informed task performances of patients and roughly indicated functional areas of interest. In our preliminary experience, 100% sensitivity and specificity of HGA mapping suggests that it would be gold standard for functional mapping during awake craniotomy. By contrast, the characteristic "HGA dynamics" should be carefully addressed for future studies. HGA mapping revealed language-related activity only in the frontal region so far. These findings are valuable for understanding functional dynamics of the human brains.

Although ECS is still gold standard, it requires longer investigation times and adequate tasks and stimulus intensities. A method that uses preoperative fMRI and neuronavigation has been developed to overcome these issues. Five reports have investigated the sensitivity and specificity of language-related fMRI using ECS in patients during awake craniotomies (2, 12, 14, 20, 31). Most of these studies used a high magnetic–field MR scanner and PN tasks. Their sensitivity and specificity values, however, varied (59%–100% and 56%–97%, respectively), because of the inherent limitations of ECS such as the limits on the investigation time, the number of available tasks, and physiological differences.

In the present setting, fMRI, which detects blood flow changes, had hemodynamic delay and different energy consumptions over the language areas. Those physiological differences between them would cause discrepancy of the results. Kunii et al. (19, 20) have given an answer for the inquiry, using chronically implanted subdural electrodes and multiple semantic tasks with ECS mapping to investigate patients in conditions that are less invasive than awake craniotomy. Although WR-fMRI showed significant activation in all the patients, the results demonstrated that the greatest sensitivity and specificity were 91% and 58%, respectively, and were observed only in the frontal region. Their results did not produce reliable language maps, and these authors found anatomical and functional discrepancies between the results of fMRI and ECS mapping for the frontal and temporal lobes. They concluded that brain oscillations, such as event related synchronization, might be the key to interpret the basic neurophysiology of each technique.

Sanai and Berger et al. (33) proposed a new mapping procedure they termed "negative mapping." According to their surgical experiences with 145 cases, a general and practical issue is that exposed brain areas might be insufficient for detecting

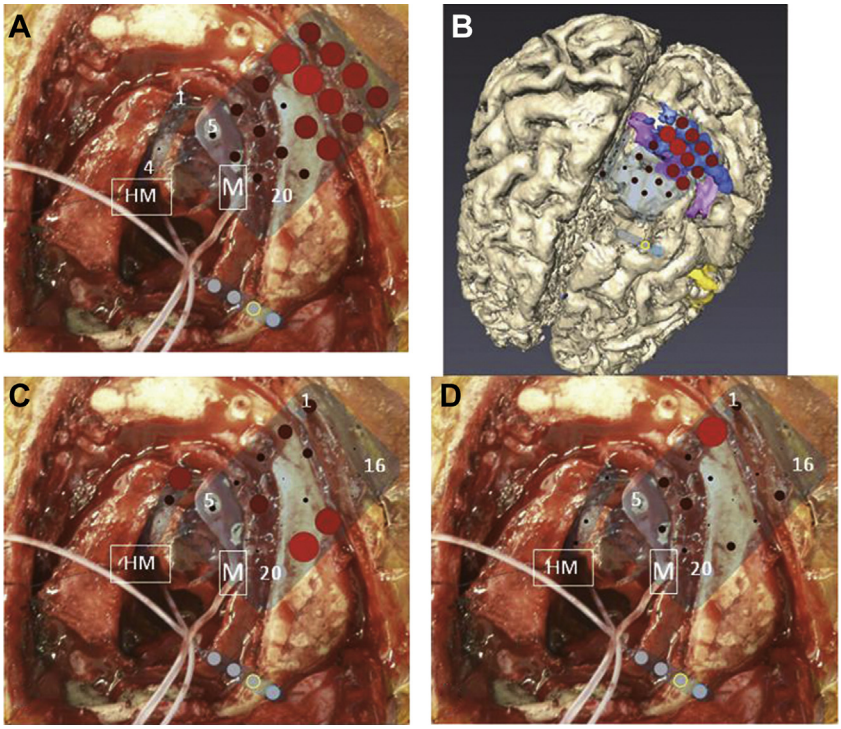


**Figure 6.** Functional localization for patient 3. (**A**) Real-time high gamma activity (HGA) mapping by finger-tapping (FT) task showing significant HGA increase (10 red circles) in the motor and somatosensory cortices. (**B**) Three-dimensional reconstructed magnetic resonance imaging (MRI) demonstrating widespread activation of FT-functional MRI, which was similar with FT-HGA. (**C**) Real-time HGA mapping by ankle movement task showing scattered red circles in HM4 of the medical frontal region and M18 and 19 of the primary motor cortex. (**D**) Real-time HGA mapping by word reading task demonstrating little HGA activation except in M2 on the parietal lobe.

positive language sites. Therefore, craniotomies should limit the cortical exposure, even without the localization of positive language sites, to permit aggressive lesion resection without producing language deficits. Although "negative mapping" is now widely accepted, neurosurgeons still need to perform appropriate ECS to confirm positive and negative functional areas. Because our final goal was to quickly perform brain mapping without ECS, we focused on detecting neurophysiological signals directly from the brain surface. As a result, we observed motor- and language-related HGA on the brain surface and unexposed cortices by inserting electrode grids and strips. We believe that real-time HGA mapping should be an additional technique to "negative mapping" and expect that it will be the gold standard to identify functional centers, which may finally allow us to skip ECS.

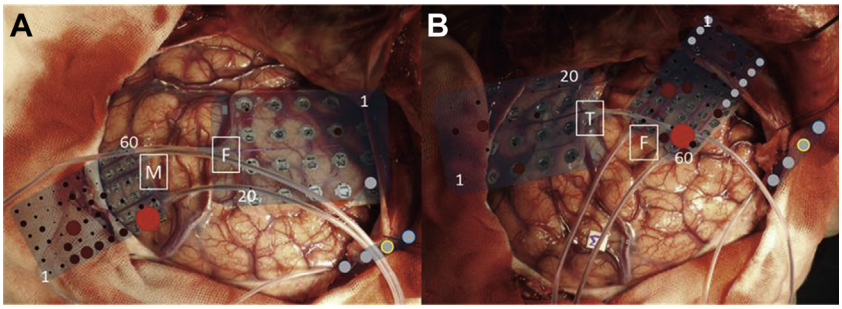


**Figure 7.** Functional localization for patient 4. Remarkably, a 60-channel grid was used for functional mapping. (**A**) A 60-channel grid was used on motor area (M), and a 20-channel grid was used on frontal area (F). Real-time high gamma activity (HGA) mapping by finger-tapping task showing significant HGA increase (*red circle* of M9) in the primary motor cortex. (**B**) A 60-channel grid was used on frontal lobe (F), and a 20-channel grid was used on temporal lobe (T). Real-time HGA mapping by word reading task demonstrating significant HGA increase (*red circle* of F49) in the frontal lobe.

In this study, we focused on high-frequency oscillation because previous reports using chronic subdural grids stated that HGA accumulation indicated eloquent centers better than the other frequency components. HGAs show strong correlations with a variety of functional domains, including motor (24, 25), auditory (6, 9, 41), visual (22, 40), language (7, 23, 43), and episodic memory (36). Roland et al. (30) investigated 2 cases (one with right-sided and other with left-sided lesion) with ECoG recordings during an awake craniotomy. Their results showed good agreement in the motor function in HGA and ECS mapping. However, the results of HGA mapping in the language-related function were insufficient. Their HGA mapping showed mainly mouth-motor activations even by the PN task. Our study focused on patients with left-sided lesions and confirmed language localization in the frontal region. As a result, real-time HGA mapping showed perfect agreements with ECS mapping by combining semantic tasks. The proposed technique would be clinically useful, but it would necessitate selecting patients and applying appropriate tasks depending on lesion locations by combining with preoperative fMRI. Cardin et al. (3) suggested that HGA should be generated by synchronous postsynaptic potentials of fast-spiking GABAergic interneurons incorporated in a cortical assembly. In addition, approximately 74% of the brain's energy budget was estimated to be devoted to postsynaptic potentials (1). Thus, HGA could account for a large part of blood oxygenation changes. In this study, we found that HGA mapping precisely indicated frontal language areas, where parts of language-fMRI activation appeared.

As mentioned previously, we encountered limitations with identifying temporal language activation in HGA and fMRI results. Although our previous work revealed a positive correlation between HGA and fMRI signals in language-related cortices,

the results of the present study revealed that different temporal profiles of HGA in the frontal and temporal lobes, which explained the spatial dissociation of HGA and fMRI signals (19). We emphasized that frontal HGA lasted much longer than temporal HGA during the WR task. In this study, real-time HGA mapping demonstrated a rapid regression of the temporal HGA, whereas slow and long-lasting frontal HGA was induced by language-related tasks. Because we integrated HGA for at least 60 seconds, the longer-lasting frontal HGA might remain and the fundamental differences of HGA dynamics might help clarify the underlying neurophysiological mechanisms.

The critical issue of this technique was electrical noise in the operation theaters. Our recording system uses a computer, which controlled stimulus-triggered conditions and acquired ECoG data with a closed loop to avoid unnecessary alternative current noise. Direct current noise was much greater than alternative current noise in amplitude and exceeded the amplifier dynamic ranges of g.HIamp. Because direct current noise was generated by depolarization, we used the same material for the reference electrode that was used for the subdural recording grids. As a result, we succeeded in extracting HGA-induced activity by tasks during an awake craniotomy.

We used common subdural grids that had 3-mm diameters and 10-mm interchannel distances. These parameters resulted in a relatively low-resolution mapping. From the surgical point of view, we might be able to resect lesions more precisely. To obtain finer and more reliable functional distributions with real-time HGA mapping, we need to develop high-resolution ECoG electrodes with smaller diameters and interchannel distances. It would be possible to elucidate the intergyrus functional gradation and dynamics. Further verification with a larger sample size is needed to clarify variations in the functional distribution, task-dependent findings, and inter-patient differences. We believe that the proposed technique has great potentials to make rapid and precise functional mapping for awake craniotomies.

## CONCLUSION

We demonstrated the clinical impact of real-time HGA mapping and functional neuronavigation during an awake craniotomy. Their combination contributed to rapid and accurate identification of motor and frontal language centers. This novel technique enables physicians to make functional brain mapping rapidly, thereby skipping the ECS procedure. Furthermore, real-time HGA mapping sheds light on the underlying physiological mechanisms related to greater brain functions.

## REFERENCES

1. Attwell D, Iadecola C: The neural basis of functional brain imaging signals. Trends Neurosci 25: 621-625, 2002.
2. Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, Aquino D, Marras C, Caldiroli D, Broggi G: Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology 248:579-589, 2008.
3. Cardin JA, Carlen M, Meletis K, Knoblich U, Zhang F, Deisseroth K, Tsai LH, Moore CI: Driving fast-spiking cells induces gamma rhythm and controls sensory responses. Nature 459: 663-667, 2009.
4. Catani M, Jones DK, ffytche DH: Perisylvian language networks of the human brain. Ann Neurol 57:8-16, 2005.
5. Conner CR, Ellmore TM, Pieters TA, DiSano MA, Tandon N: Variability of the relationship between electrophysiology and BOLD-fMRI across cortical regions in humans. J Neurosci 31:12855-12865, 2011.
6. Crone NE, Boatman D, Gordon B, Hao L: Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001. Clin Neurophysiol 112:565-582, 2001.
7. Crone NE, Hao L, Hart J Jr, Boatman D, Lesser RP, Irizarry R, Gordon B: Electrocorticographic gamma activity during word production in spoken and sign language. Neurology 57: 2045-2053, 2001.
8. Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno D: Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. Brain 125:199-214, 2002.
9. 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 94:4269-4280, 2005.
10. Ekstrom A: How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. Brain Res Rev 62:233-244, 2010.
11. Fernandez G, Specht K, Weis S, Tendolkar I, Reuber M, Fell J, Klaver P, Ruhlmann J, Reul J, Elger CE: Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. Neurology 60:969-975, 2003.
12. FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, Rosen BR, Benson RR: Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. AJNR Am J Neuroradiol 18:1529-1539, 1997.
13. Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R: Analysis of fMRI time-series revisited. Neuroimage 2:45-53, 1995.
14. Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C: Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. Neurosurgery 66:113-120, 2010.
15. Hermes D, Miller KJ, Vansteensel MJ, Aarnoutse EJ, Leijten FS, Ramsey NF: Neurophysiologic correlates of fMRI in human motor cortex. Hum Brain Mapp 33:1689-1699, 2012.
16. Kamada K, Sawamura Y, Takeuchi F, Houkin K, Kawaguchi H, Iwasaki Y, Kuriki S: Gradual recovery from dyslexia and related serial magnetoencephalographic changes in the lexicosemantic centers after resection of a mesial temporal astrocytoma. Case report. J Neurosurg 100: 1101-1106, 2004.
17. Khursheed F, Tandon N, Tertel K, Pieters TA, Disano MA, Ellmore TM: Frequency-specific electrocorticographic correlates of working memory delay period fMRI activity. Neuroimage 56: 1773-1782, 2011.
18. Kruggel F, von Cramon DY: Temporal properties of the hemodynamic response in functional MRI. Hum Brain Mapp 8:259-271, 1999.
19. Kunii N, Kamada K, Ota T, Greenblatt RE, Kawai K, Saito N: The dynamics of language-related high-gamma activity assessed on a spatially-normalized brain. Clin Neurophysiol 124: 91-100, 2013.
20. Kunii N, Kamada K, Ota T, Kawai K, Saito N: A detailed analysis of functional magnetic resonance imaging in the frontal language area: a comparative study with extraoperative electrocortical stimulation. Neurosurgery 69:590-596; discussion 596-597, 2011.
21. Lachaux JP, Fonlupt P, Kahane P, Minotti L, Hoffmann D, Bertrand O, Baciu M: Relationship between task-related gamma oscillations and BOLD signal: new insights from combined fMRI and intracranial EEG. Hum Brain Mapp 28: 1368-1375, 2007.
22. Lachaux JP, George N, Tallon-Baudry C, Martinerie J, Hugueville L, Minotti L, Kahane P, Renault B: The many faces of the gamma band response to complex visual stimuli. Neuroimage 25:491-501, 2005.
23. Lachaux JP, Jung J, Mainy N, Dreher JC, Bertrand O, Baciu M, Minotti L, Hoffmann D, Kahane P: Silence is golden: transient neural deactivation in the prefrontal cortex during attentive reading. Cereb Cortex 18:443-450, 2008.
24. Lesser RP, Arroyo S, Crone N, Gordon B: Motor and sensory mapping of the frontal and occipital lobes. Epilepsia 39 (Suppl 4):S69-80, 1998.

25. Leuthardt EC, Miller K, Anderson NR, Schalk G, Dowling J, Miller J, Moran DW, Ojemann JG: Electrocorticographic frequency alteration mapping: a clinical technique for mapping the motor cortex. Neurosurgery 60:260-270; discussion 270-261, 2007.

26. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A: Neurophysiological investigation of the basis of the fMRI signal. Nature 412: 150-157, 2001.

27. Nir Y, Fisch L, Mukamel R, Gelbard-Sagiv H, Arieli A, Fried I, Malach R: Coupling between neuronal firing rate, gamma LFP, and BOLD fMRI is related to interneuronal correlations. Curr Biol 17:1275-1285, 2007.

28. Pouratian N, Bookheimer SY, Rex DE, Martin NA, Toga AW: Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. J Neurosurg 97:21-32, 2002.

29. Prueckl R, Kapeller C, Potes C, Korostenskaja M, Schalk G, Lee KH, Guger C: cortiQ - Clinical software for electrocorticographic real-time functional mapping of the eloquent cortex. Conf Proc IEEE Eng Med Biol Soc 2013:6365-6368, 2013.

30. Roland J, Brunner P, Johnston J, Schalk G, Leuthardt EC: Passive real-time identification of speech and motor cortex during an awake craniotomy. Epilepsy Behav 18:123-128, 2010.

31. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I: Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery 52:1335-1345; discussion 1345-1337, 2003.

32. Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW: Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. Ann Neurol 51:350-360, 2002.

33. Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. N Engl J Med 358:18-27, 2008.

34. Scarabino T, Giannatempo GM, Popolizio T, Tosetti M, d'Alesio V, Esposito F, Di Salle F, Di Costanzo A, Bertolino A, Maggialetti A, Salvolini U: 3.0-T functional brain imaging: a 5-year experience. Radiol Med 112:97-112, 2007.

35. Scheeringa R, Fries P, Petersson KM, Oostenveld R, Grothe I, Norris DG, Hagoort P, Bastiaansen MC: Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron 69:572-583, 2011.

36. Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, McCarthy DC, Brandt A, Tully MS, Kahana MJ: Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cereb Cortex 17:1190-1196, 2007.

37. Serletis D, Bernstein M: Prospective study of awake craniotomy used routinely and non-selectively for supratentorial tumors. J Neurosurg 107:1-6, 2007.

38. Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, Maggio WW: Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. J Neurosurg 91:787-796, 1999.

39. 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 128:1556-1570, 2005.

40. Tanji K, Suzuki K, Delorme A, Shamoto H, Nakasato N: High-frequency gamma-band activity in the basal temporal cortex during picture-naming and lexical-decision tasks. J Neurosci 25: 3287-3293, 2005.

41. 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 32:790-798, 2006.

42. Veltman DJ, Friston KJ, Sanders G, Price CJ: Regionally specific sensitivity differences in fMRI and PET: where do they come from? Neuroimage 11:575-588, 2000.

43. Wu HC, Nagasawa T, Brown EC, Juhasz C, Rothermel R, Hoechstetter K, Shah A, Mittal S, Fuerst D, Sood S, Asano E: gamma-oscillations modulated by picture naming and word reading: intracranial recording in epileptic patients. Clin Neurophysiol 122:1929-1942, 2011.

*Conflict of interest statement: This work was supported in part by a grant from the Suhara Memorial Foundation, Grant-in-Aid No. 24390337 for Scientific Research (B) from the Japan Society for the Promotion of Science, Japan, and a Grant-in-Aid for Exploratory Research No. 26670633 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.*

*Received 26 January 2014; accepted 6 August 2014; published online 7 August 2014*

*Citation: World Neurosurg. (2014) 82, 5:912.e1-912.e10.*
*http://dx.doi.org/10.1016/j.wneu.2014.08.009*

*Journal homepage:* ***www.WORLDNEUROSURGERY.org***

*Available online:* ***www.sciencedirect.com***

*1878-8750/$ - see front matter* 