Rapid and Low-invasive Functional Brain Mapping by Realtime Visualization of High Gamma Activity for Awake Craniotomy

K Kamada, H Ogawa, C Kapeller, R Prueckl, C Guger

Abstract— **For neurosurgery with an awake craniotomy, the critical issue is to set aside enough time to identify eloquent cortices by electrocortical stimulation (ECS). High gamma activity (HGA) ranging between 80 and 120 Hz on electrocorticogram (ECoG) is assumed to reflect localized cortical processing. In this report, we used realtime HGA mapping and functional magnetic resonance imaging (fMRI) for rapid and reliable identification of motor and language functions. Three 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. After the craniotomy, we recorded ECoG activity by placing subdural grids directly on the exposed brain surface. Each patient performed motor and language tasks and demonstrated realtime HGA dynamics in hand motor areas and parts of the inferior frontal gyrus. Sensitivity and specificity of HGA mapping were 100% compared to ECS mapping in the frontal lobe, which suggested HGA mapping precisely indicated eloquent cortices. The investigation times of HGA mapping was significantly shorter than that of ECS mapping. Specificities of the motor and language-fMRI, however, did not reach 85%. The results of HGA mapping was mostly consistent with those of ECS mapping, although fMRI tended to overestimate functional areas. This novel technique enables rapid and accurate functional mapping.**

I. INTRODUCTION

Language functions are generated through complex neural networks. To improve our understanding of language mechanisms, it is necessary to construct detailed brain maps using functional imaging and electrophysiological techniques. On the other hand, maximal resection of brain tumors from eloquent areas carries high risks of neurological consequences such as deficits of motor and language functions. It is, therefore, indispensable to identify and preserve the eloquent cortices and subcortical connections from surgical injury [1]. Several groups have proposed that electrocortical stimulation (ECS) during an awake craniotomy is a reliable way to perform brain mapping [2],[3],[4]. However, technical difficulties for this method remain, such as risks of epileptic seizures, identifying optimal stimulation sites, and producing unintended neurological deficits during the procedure. There are two practical and less invasive techniques than ECS that can identify the 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 two decades[1],[5],[6]. Higher order cognitive functions such as language seem to have wider activation areas on fMRI than what can be revealed with ECS mapping [6]. Power changes in oscillatory neuronal activity within various frequency ranges revealed with electrocorticogram (ECoG) have recently received attention as a potential physiological correlate of BOLD responses [7],[8]. Among these oscillatory changes, augmentation of high gamma activity (HGA) ranging approximately 60–140 Hz is assumed to reflect localized cortical processing. Crone et al. constructed HGA maps that indicated language-related functions from patients performing word reading tasks [3]. 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 realtime HGA mapping and fMRI-based functional neuronavigation during an awake craniotomy and demonstrate the clinical impact of this novel method in our representative experiences.

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K. Kamada and H. Ogawa are with the Department for Neurosurgery, Asahikawa Medical University, Asahikawa, Japan. (Corresponding author: K. Kamada. Phone: 81-166-68-2594;fax: 81-166-68-2599 e-mail:kamady-k@umin.ac.jp).

C. Kapeller, C. R. Prückl and C. Guger are with g.tec Guger Technologies OG, Schiedlberg, Austria.

II. MATERIALS AND METHODS

A *Patients*

Three 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 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.

TABLE 1 DEMOGRAPHIC DATA OF PATIENTS

Case No.	*Tumor location*	*Symptoms*	*Pathological diagnosis*
1	Left front-temporal lobe	Dysarthria	Glioblastoma
2	Left parietal lobe	Dysarthria	Glioblastoma
3	Left frontal lobe	Mild right hemiparesis	Anaplastic astrocytoma

B *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, WI, USA). We performed fMRI with a

T2-weighted echo-planar imaging sequence and each fMRI session consisted of three dummy scan volumes, three activation periods, and four baseline (rest) periods. During each period, five 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.

functional MRI tasks

Hand grasping (HG) task: During the active period of the hand grasping (HG) task, patients were asked to perform HG in response to auditory pacing cues. During the rest period, patients concentrated on their heart beat without movement.

Word reading (WR) task: During the active periods, words consisting of three Japanese letters were presented for 2000 ms and interleaved between 500-ms interstimulus intervals. The patients were instructed to silently categorize the presented word as either abstract or concrete. 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: Patients were instructed to silently name the objects presented in color illustrations. 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.

MR postprocessing and analysis

After MR data acquisition, the fMRI data of each patient were analyzed with the standard general linear model (GLM) 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 anatomical MRI and transferred to a neuronavigation system.

C *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). 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 (Guger Technologies OG).

For the intraoperative ECoG recordings, each patient was first asked to be relaxed for 20 s for the rest period (baseline) and then perform the HG task as it was performed for active period by hand grasping for 20 s. The baseline and active phases were performed 3 times in this order, for a total of 2 min. Patients then performed the same language tasks that 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 realtime processing system driven by the g.HIamp. For the WR task, the patient read aloud Japanese words. ECoG measurements were repeated during the WR task to confirm their reproducibility. In the PN task, the patients overtly named the objects. In order to obtain the baseline ECoG, the patients passively viewed destructured words or 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 in MATLAB R2012a (Mathworks; Natick, MA, USA), which ran on the data acquisition computer that acquired data from the g.HIamp via USB [9]. CortiQ performed a common average reference (CAR) to suppress common mode signals and calculated the baseline ECoG activity of each channel in the gamma frequency range 80–120 Hz. Fast Fourier transformation were performed every 1 Hz using 250 ms windows with 125ms step sizes to obtain power spectral density estimates. A Hanning window was imposed on each data window to attenuate edge effects. To obtain power averages across HGA, we standardized the power spectral density values with respect to 20 s × 3 ECoG data epochs that 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. Finally, the results were visualized in realtime in the MATLAB environment as circles overlaying the electrode. The significance value was represented by the circle's diameter. The computations were performed in real time and updated at 20 Hz.

D *Electrocortical stimulation mapping*

After the ECoG recording, a biphasic electrical pulse (frequency, 50 Hz; pulse duration, 1 ms) was applied to the brain using a bipolar electrode with 10 mm between tips. 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. 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. 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 in naming.

III. Results

Patient symptoms and task performance

All patients showed little impairment of language functions. fMRI during the HG task clearly indicated increased activity in the hand motor representation in all cases (see Figure. 1). During the WR and PN tasks, fMRI in all cases revealed a clear language lateralization and activated pixel clusters mainly in the inferior (IFG) and middle frontal gyri (MFG), the dorsolateral prefrontal cortex. On the basis of the fMRI results, we were confident that the patients would be able to perform the tasks during awake craniotomy.

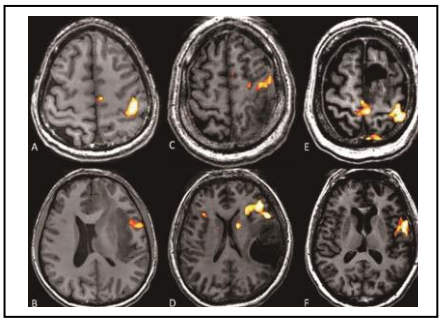

Figure 1: fMRI by HG (A) and WR (B) tasks of case 1 showing task-related activations in the primary hand-motor cortex and inferior frontal gyrus, respectively. C. fMRI by HG task of case 2. D fMRI by WR task of case 2.E fMRI by HG task of case 3 showing wide-spread motor-related activations. F fMRI by WR task of case 3 delineating the frontal language activations.

Intraoperative ECoG recording

After performing the craniotomy, we confirmed the patient was awake and could easily follow verbal commands and answer simple questions. During operation, we observed obvious ECoG changes between rest and active periods

Case 1: The ECoG recorded a significant HGA increase with HG task in two channels that corresponded to the hand motor area (HG-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 (see Figure 2). ECS applied to the HG-HGA area (channels M11 and M12) evoked a muscle contraction in the right hand. ECS applied to the WR- and PN-HGA areas (channel F9) consistently evoked speech arrest or naming difficulty.

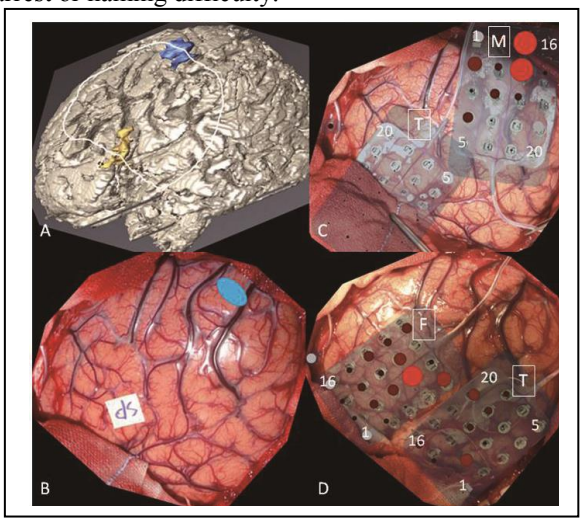

Figure 2: A: 3D reconstructed MRI including fMRI activations showing craniotomy (white circle), FT-fMRI activations (blue), and WR-fMRI activations (yellow). Note that craniotomy exposed the primary motor and frontal language areas. B: Results of electrocortical stimulation validating the primary hand-motor cortex (blue) and frontal language area (a tag of "SP"). C: Realtime high gamma activity (HGA) mapping by FT task showing significant HGA increase (red circles of M11 and 12) in the primary motor cortex. D: Realtime-HGA mapping by WR task showing significant HGA increase (a red circle of F9) in the inferior frontal gyrus.

Sensitivity and specificity of HG-, PN- and WR-HGA mapping were 100% and 100% compared to ECS mapping, respectively. Although sensitivities of HG- and all langauge-fMRI were 100%, specificities of HG-fMRI and language-fMRI were 81.6% and 80.6%, respectively. Language-fMRI activations were larger, but involved WR- and PN-HGA areas. Realtime 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 HG, WR, and PN in all patients. Although HG-HGA appeared consistently only on two electrodes, WR-HGA was visible approximately 10 s into the first active period for channels T9, T13, T14, and T15 (Figure 5A) of the superior temporal gyrus, but immediately diminished. The frontal region showed longer WR-HGA activation on channels F5, F9, and F11 (Figure 3A), 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 was in contrast to the short activation observed for the superior and middle temporal lobes (see Figure 3).

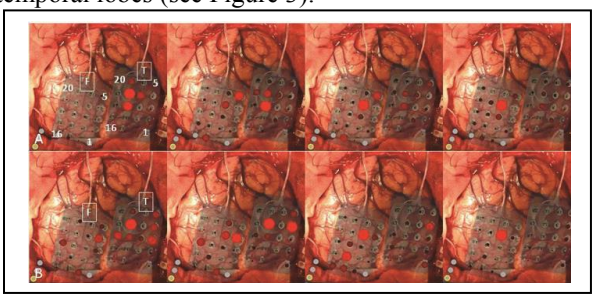

Figure 3: HGA dynamics related to WR (A) and picture naming (PN)(B) tasks. Each frame shows HGA profiles at 5, 10, 15 and 20sec, respectively. Note transient HGA appeared in the initial frames on the temporal lobe. The frontal HGA (a red circle of F9) remained at 20 sec after the task initiation.

After tumor resection, the patient suffered from transient motor-dominant aphasia for a week.

Case 2: In patient 2, two electrodes of HG-HGA clearly indicated the hand motor area. WR-HGA appeared in four channels on IFG, suggesting that the exposed cortex that included the tumor did not mediate language functions. ECS applied to the localized HG-HGA area initially showed hand muscle contractions, but subsequently caused a generalized seizure. HG- and language-fMRI results were validated by ECS, HG-HGA, and language-HGA. Sensitivity and specificity of HG- and WR-HGA mapping were 100% and 100% compared to ECS mapping, respectively. On the other hand, those of HG-fMRI were 100% and 76.3%, which indicated fMRI activation was much wider in extent. Sensitivity and specificity of language-fMRI were 100% and 64.2%, respectively.

Case 3: HG-HGA was apparent in more than six channels that covered the hand motor area, the somatosensory cortex, and the surrounding regions under the dura matter. The wide HG-fMRI activations around the hand-motor area were similar with HG-HGA in size (Figure 4A, B). One channel of the inserted strip electrode (channel HM 1, Figure 4C) 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 4C). WR-, 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 4D) because the electrodes did not reach the frontal language area. We confirmed the HG-HGA by ECS and sensitivity and specificity of HG-fMRI were 100% and 70%, respectively. His postoperative condition was uneventful except a transient weakness of the right lower extremity (see Figure 4)

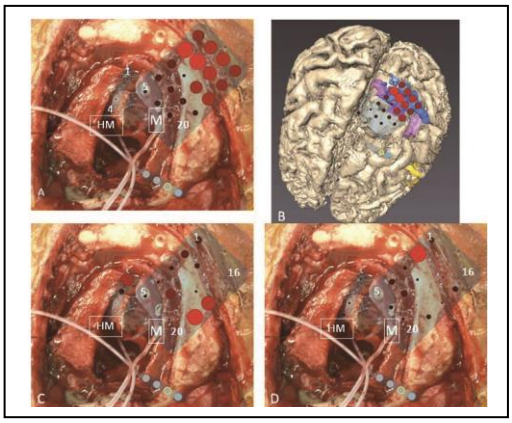

Figure 4: A: A Realtime HGA mapping by FT task showing significant HGA increase (10 red circles) in the motor and somatosensory cortices in case 3. B 3D reconstructed MRI demonstrating wide-spread activation of FT-fMRI, which was similar with FT-HGA. C Realtime HGA mapping by ankle movement task showing scattered red circles in HM4 of the medical frontal region and M18 and 19 of the primary motor cortex. D Realtime HGA mapping by WR task demonstrating little HGA activation except in M2 on the parietal lobe.

We calculated investigation times of HGA and ECS mapping in all the cases. The investigation time was 9.3 ± 2.3 min for HGA mapping, whereas 26.3 ± 8.0 min for ECS mapping (P= 0.046 <0.05). There was significant difference between the two procedures

Postoperative MRI demonstrated total removal of the enhancing lesion in all the cases.

IV Discussion

We have demonstrated a novel technique that uses realtime HGA mapping during awake craniotomies. This procedure has the following advantages: it is noninvasive, it facilitates significant shortening of the duration of cortical mapping and detecting functional representations for cortical regions hidden under dura mater, and it avoids the risk of seizure or brain damage during awake craniotomies. In our experience, both neurosurgeons and patients have taken considerable steps toward less invasive lesion resection. The ECoG analysis revealed enhanced language-related activity in only the frontal region. These findings are valuable for understanding functional dynamics of the human brains. 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, auditory, visual, language, and episodic memory. As mentioned above, we encountered limitations with identifying temporal language activation in HGA results. We suspected that frontal HGA lasted much longer than temporal HGA during the WR task according to the results and our previous study [7]. 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. In order to obtain finer and more reliable functional distributions with realtime HGA mapping, we need to develop high-resolution ECoG electrodes with smaller diameters and interchannel distances. It would be possible to elucidate the inter-gyrus functional gradation and dynamics. Further verification with a larger sample size is needed to clarify variations in the functional distribution, task-dependent findings, and interpatient differences. We believe that the proposed technique has great potential for awake craniotomies.

Conclusions

We demonstrated the clinical impact of realtime 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 less invasive, thereby skipping the ECS procedure. Furthermore, realtime HGA mapping sheds light on the underlying physiological mechanisms related to higher brain functions.

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