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Case Report

Passive real-time identification of speech and motor cortex during an awake craniotomy

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ABSTRACT

Precise localization of eloquent cortex is a clinical necessity prior to surgical resections adjacent to speech or motor cortex. In the intraoperative setting, this traditionally requires inducing temporary lesions by direct electrocortical stimulation (DECS). In an attempt to increase efficiency and potentially reduce the amount of necessary stimulation, we used a passive mapping procedure in the setting of an awake craniotomy for tumor in two patients resection. We recorded electrocorticographic (ECoG) signals from exposed cortex while patients performed simple cue-directed motor and speech tasks. SIGFRIED, a procedure for real-time event detection, was used to identify areas of cortical activation by detecting task-related modulations in the ECoG high gamma band. SIGFRIED's real-time output quickly localized motor and speech areas of cortex similar to those identified by DECS. In conclusion, real-time passive identification of cortical function using SIGFRIED may serve as a useful adjunct to cortical stimulation mapping in the intraoperative setting.

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1. Introduction

An unresolved challenge in the practice of neurosurgery is to identify and avoid injury to eloquent areas of the brain that may lead to permanent neurological deficit if disturbed. The interindividual variation in functional anatomy mandates extensive cortical mapping prior to surgical resection of lesions located adjacent to eloquent cortex [1]. The gold standard for cortical mapping, direct electrocortical stimulation (DECS), has a long history of application in the practice of neurosurgery. Its utility in improving functional outcomes in glioma surgery has been demonstrated [2], but potential side effects remain a significant concern. Specifically, afterdischarges, seizures, and distant site stimulation may result in false information leading to complete failure of the procedure or other morbidities. Intraoperative stimulation-induced seizures can be seen in 1.2–9.5% of patients, depending on the type of stimulation used [3], Although several less invasive alternatives to DECS have been explored, such as fMRI [4] and PET [5], they are not yet practical enough for widespread routine use. Furthermore, technical constraints further impede the utility of these methods in the intraoperative setting. In this study, we demonstrate the first use of a real-time mapping procedure called SIGFRIED [6], which is based on passive electrocorticography (ECoG). This procedure may serve as an adjunct to DECS such that the operating neurosurgeon can target direct cortical stimulation to the most relevant areas first. Thus, this technique may reduce morbidity and increase the efficiency of intraoperative cortical stimulation mapping.

The brain generates oscillating electrical potentials at a broad range of frequencies that show characteristic task-related changes. Commonly, these have been described in the context of sensorimotor cortical activation. The notable frequencies comprise mu (8–12 Hz), beta (18–26 Hz), and gamma (>30 Hz) oscillations [7–9]. The lower frequencies of mu and beta are thought to be produced by thalamocortical circuits that decrease in amplitude in association with actual or imagined movements [10–13]. In general, these changes in lower-frequency bands tend to have a large spatial distribution and, hence, are only modestly specific to the type of function. Activity in gamma frequencies (>30 Hz) is thought to be produced by smaller cortical circuits [14]. These frequencies increase in amplitude with cortical activation and tend to have a more cortically focal anatomic distribution for signal change. On a functional level, several studies have revealed that higher frequencies carry highly specific information about cortical processing with respect to speech, motor movements, and motor intention [15–19]. Changes in these frequency rhythms have been used in offline analyses for brain mapping [16,17,20] and compared with the gold standard of DECS [18,21,22]. Although these studies demonstrated the general feasibility of passive functional mapping, the methods used required expertise in signal analysis and cortical physiology and, thus, were not readily applicable in clinical settings.

A procedure known as SIGFRIED (signal modeling for real-time identification and event detection) has recently been developed for

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motor and speech mapping during extraoperative brain mapping [6] to reduce this need for expert oversight. SIGFRIED accomplishes increased efficiency of localization by implementing a detection-based approach based on a gaussian mixture model of recorded brain signals. Rather than using a discrimination-based approach, where an active condition is alternated with a rest condition and then subsequently analyzed, SIGFRIED creates a statistical model of baseline brain activity and then subsequently detects significant deviations from that baseline. This is done in an automated process that does not require the definition of any signal processing parameters by the clinician. The process requires three steps: (1) recording a baseline signal in the absence of overt motor or speech activity, (2) building a statistical model based on the baseline signal, and (3) detecting significant differences from the baseline signal model during cue-directed activity. This enables a real-time assessment of cortical changes that is shown on a topographical display and, as a result, obviates the need for post hoc analysis by an expert. This software is based on the BCI2000 software suite [23], a general-purpose brain–computer interface system for data acquisition, stimulus presentation, and cortical monitoring. It supports acquisition from a number of hardware devices, can process different types of brain signals, and can relay the output to a variety of devices. In the context of brain mapping, it supports programmable presentation of auditory/visual stimuli and receipt of device input. BCI2000 associates the timing of these stimuli with recorded ECoG signals, which facilitates time-locked analyses. The combination of SIGFRIED and BCI2000 has been shown to be useful in the extra-operative setting for localization of eloquent cortex with implanted subdural electrode arrays [24].

Thus far, the use of real-time passive ECoG mapping has not been reported in the setting of awake craniotomies. Because of the short times required for mapping, the real-time identification of functional sites, and the automated nature of the process, the SIGFRIED methodology is well suited to the needs of intraoperative cortical mapping. Here we demonstrate for the first time the application of SIGFRIED in the setting of an awake craniotomy for cortical mapping prior to tumor resection. We report two cases in which passive mapping with SIGFRIED successfully identified areas of cortex associated with hand motor, tongue motor, and speech activity. These data were available to the surgeon within minutes. Additionally, these passively identified speech and motor loci correlated well with sites identified with standard DCES. In summary, our preliminary experience suggests that SIGFRIED can be used practically and with good results in the intraoperative setting. Because of its ease of use and encouraging results, SIGFRIED may find wide adoption by neurosurgeons in the future.

2. Methods

Two patients with brain tumors localized to eloquent cortex underwent standard awake craniotomies with cortical mapping and tumor resection (Fig. 1). After initial dural opening and hemostasis, an ECoG electrode array (Ad-Tech, Racine, WI, USA) was placed on the surface of the brain to record cortical surface potentials. The array was covered by wet lap pads to prevent movement of the array during mapping and maintain contact between the electrodes and the cortical surface. The array consisted of 48 platinum electrodes embedded in Silastic and arranged in a 6×8 rectangular grid. The electrodes were 4 mm in diameter, with 2.3 mm exposed and 1-cm interelectrode spacing. The electrode leads were connected to three optically isolated 16-channel USB biosignal amplifiers. A similarly configured six-electrode strip was placed at a distant site for use as a ground and reference channel. The signal was sampled at 1200 Hz and collected by a Dell Optiplex computer (Dell, Houston, TX, USA) running the BCI2000 [23] and SIGFRIED software [6].

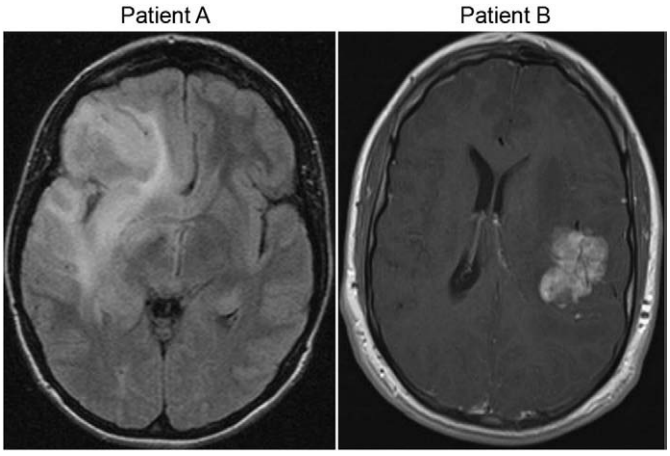

Fig. 1. Clinical MRI scans. Axial MRI images of patient A's right frontotemporal tumor and patient B's left parietal tumor.

Once each patient was deemed awake and cooperative, we recorded 6 minutes of rest activity using BCI2000. The software then used these data to build a model of that rest activity (i.e., one model for each location) [25]. Specifically, after re-referencing the brain signals to the common average, it then extracted spectral estimates of the 70–115 Hz band (starting at 70 Hz and with bin width 5, the last bin ends at 115 Hz) at each location using an autoregressive model. Activity in this frequency range has previously been shown useful for functional localization [22,26]. The software then fit a gaussian mixture model to the distribution of spectral estimates extracted from the baseline recording. This modeling process was fully automated and required less than 1 minute for each patient.

The patients engaged in different tasks following visual cues that were presented on an LCD monitor placed at eye level. Each trial was cued by display of the word *Hand*, *Tongue*, or *Speak* to indicate continuous opening and closing of the contralateral hand, protrusion and retraction of the tongue, and recitation of the alphabet (patient A) or part of the Pledge of Allegiance (patient B), respectively. In addition to the visual cue, an audible tone indicated the beginning and end of each trial for patient B. Each cue was presented for 15 seconds and was followed by a rest period of the same length before proceeding to the next trial (see Appendix: Supplementary Video). The three activity types proceeded in order and this sequence was repeated five times. This actual mapping procedure lasted a total of 7.5 minutes ([15 seconds + 15 seconds]$\times3\times5$/60 seconds/minute).

As the patient performed the different tasks, BCI2000 acquired signals from the g.USBamp amplifier systems. The resulting time-series ECoG signals were first re-referenced to the common average and transformed into the frequency domain using an autoregressive model. In real time, the SIGFRIED component in BCI2000 determined, for each location, the negative log likelihood that the 70- to 115-Hz spectra at that location differed from the spectral distribution during the baseline period. Finally, the software determined the coefficient of determination (r^2) between the distributions of negative log likelihood values for the task and interleaved rest periods. This procedure resulted in one r^2 value (that was continuously updated during data collection) for each location and task. These r^2 values were presented in an easily interpreted display (Fig. 2) on a second monitor. This display showed, for each task, a circle at each location whose diameter was proportional to the r^2 at that location. All of these computations were performed in real time with an update frequency of 20 Hz.

After passive identification of hand motor, tongue motor, and speech cortex, standard DECS mapping proceeded as normal. To

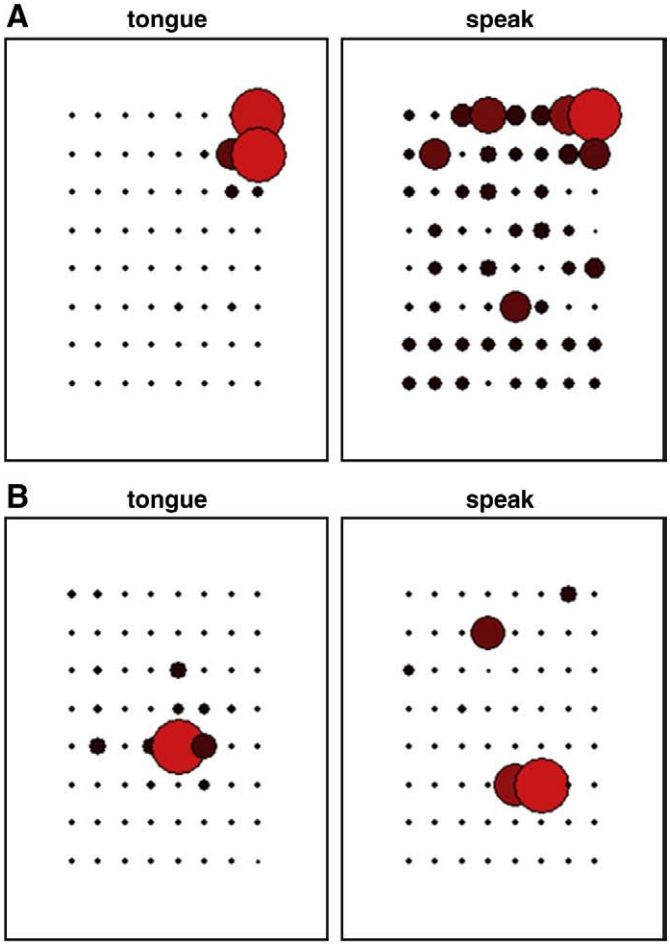

Fig. 2. SIGFRIED output. Visual representation of signal correlation with cued tongue motor (left column) and speech (right column) activity for patient A (top) and patient B (bottom). Grid numbering proceeds from left to right and top to bottom such that electrode 1 is at the top left, electrode 8 is at top right, and electrode 48 is at bottom right. Circle size and hue are proportional to the r^2 value for the given task and location.

locate speech areas, such as Broca's (Brodmann area 44/45), the patient performed a previously practiced objectnnaming task by verbally identifying objects that were presented by a laptop computer. During naming, the surgeon electrically stimulated areas of cortex and observed the patient for any functional effects. Speech areas were identified by hesitation or arrest of naming elicited by at least three separate trials of stimulation to that area. Motor areas were identified similarly by induced or inhibited movements of the hand or face after electrical stimulation.

Comparisons between sites localized with each modality were made by taking photographs of the brain surface with paper swatches that indicated the respective identified region. A stimulation site within 5 mm of an electrode location was deemed to be in the same location.

Differences in power spectra during rest and task trial periods were visualized for the 70–115 Hz frequency band used by SIGFRIED. The power spectral density (PSD) was obtained from the last 13 seconds of each task (i.e., during a speech or tongue motor task) and rest (i.e., the intertrial interval) period in 1-Hz bins using a sliding 250-ms Hann window with 50% overlap. The PSD was averaged over the five repetitions of each task and compared to the five rest periods immediately preceding the respective task. The change in power was calculated as the ratio of task to rest mean power for each electrode. Representative spectral changes are shown for SIGFRIED-positive electrodes at DECS-positive locations, as well as nearby SIGFRIED-negative electrodes at DECS-negative locations, for the tongue motor task in patient A (Figs. 3A and B, respectively) and speech in patient B (Figs. 3C and D, respectively).

3. Results

The SIGFRIED mapping procedure allowed successful identification of motor and speech cortex in both patients. Separately, with standard DECS mapping, the cortex was interrogated by DECS to determine the eloquence of the underlying cortex. In both patients, a subset of areas identified by SIGFRIED corresponded to those identified by DECS mapping for speech and motor localization.

For patient A, SIGFRIED identified moderate signal correlations (max $r^2 = 0.15$) for tongue motor activity at electrodes 8 and 16 and weak signal correlations (max $r^2 = 0.08$) for speaking at electrodes 4, 7, 8, 10, and 16 (Fig. 2A). Motor cortex was identified with DECS by eliciting tongue retraction and corresponded to electrode 8. The location of Broca's area (Brodmann area 44/45) was identified by DECS in the area corresponding to electrodes 7, 8, 15, and 16 (Fig. 4). Locations corresponding to electrodes 4 and 10, which showed weak signal correlations with speaking by SIGFRIED, did not elicit any functional speech latency or deficit with DECS. Once speech and motor cortex was sufficiently identified, tumor resection proceeded with careful preservation of the areas identified by DECS mapping. Significant resection was accomplished without postoperative speech deficit. The remainder of patient A's postoperative course was uncomplicated, and she was discharged home on postoperative day 3 at her neurological baseline.

For patient B, SIGFRIED identified moderate signal correlations (max $r^2 = 0.15$) for tongue motor activity at electrode 37 and stronger correlations (max $r^2 = 0.28$) for speaking at electrodes 12, 45, and 46 (Fig. 2B). The location of Wernicke's speech area was identified by DECS in the area corresponding to electrodes 6, 12, and 10, and that of tongue motor area at electrodes 37 and 45 (Fig. 5). Once speech and motor cortex were identified, tumor resection proceeded with careful preservation of the areas identified by DECS mapping. Significant resection was accomplished without postoperative speech deficit. The remainder of patient B's postoperative course was uncomplicated, and he was discharged home at his neurological baseline.

The tongue motor and speech sites that were identified with both methods were compared for each of the patients (Figs. 4 and 5). Of note, hand areas were mapped with the SIGFRIED method, but not expressly with DECS. Once tongue motor sites were identified, this obviated the need for further motor localization. Our results demonstrate significant regional overlap of both speech and motor sites between the SIGFRIED and DECS mapping techniques.

4. Discussion

These two cases demonstrate the technical feasibility and practicality of real-time brain mapping in the setting of an awake craniotomy for tumor resection using the BCI2000/SIGFRIED mapping system. Our results suggest that SIGFRIED is a rapid and simple means of passively identifying eloquent cortex, and that it is a useful adjunct to the current gold standard of direct electrocortical stimulation. Because this procedure is passive (i.e., does not require electrical stimulation), the state of the cortex is not affected in accruing localizing data and is not likely to interfere with current stimulation methods. Additionally, this methodology is distinct from prior passive mapping techniques [22,27] in that SIGFRIED requires no post hoc analysis, displays its results in real time, and can be easily interpreted by an operating surgeon without expertise in cortical physiology, signal analysis, or data processing.

Previous studies have examined specific cortical changes in amplitude at various frequency bands as a metric for localization of cortical activation

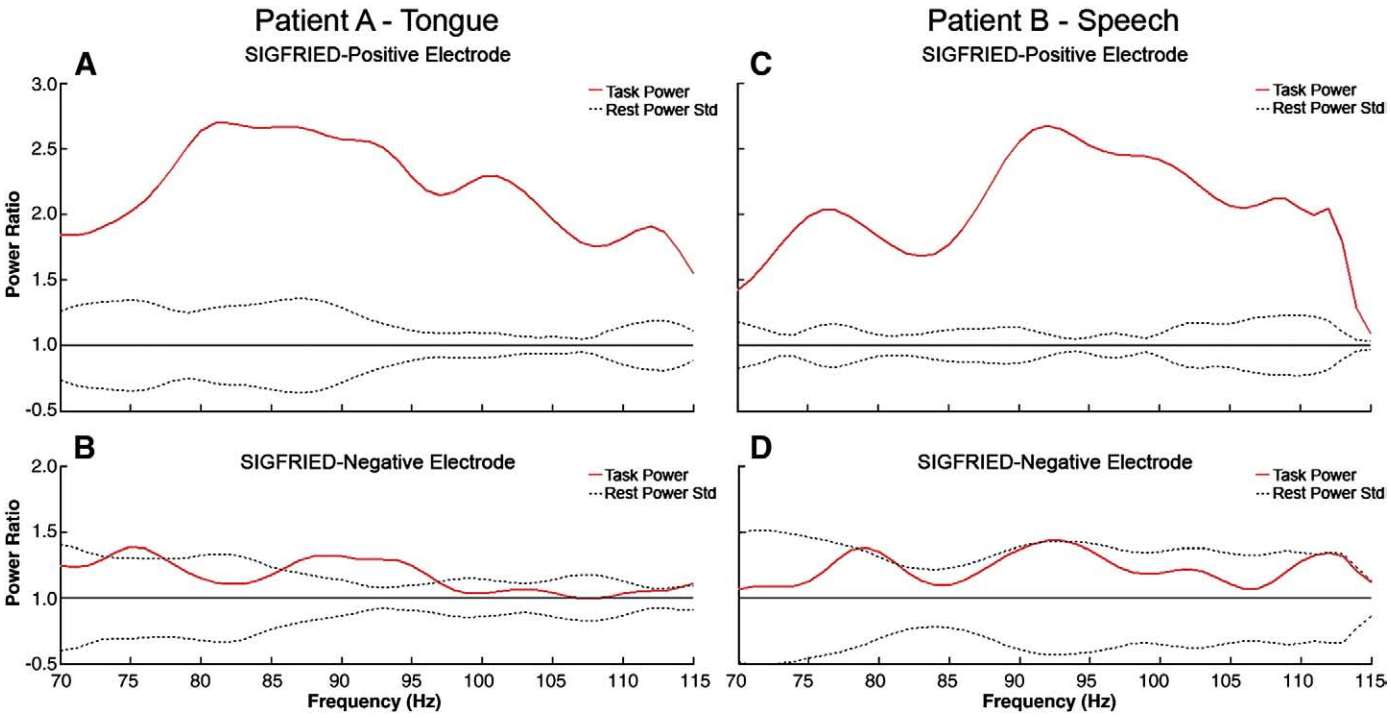

Fig. 3. Task versus rest power spectra. Representative changes in power spectral density (PSD) for SIGFRIED-positive electrodes at DECS-positive locations (A, C) as well as nearby SIGFRIED-negative electrodes at DECS-negative locations (B, D) during the tongue motor task in patient A (A, electrode 8; B, electrode 6) and speech task in patient B (C, electrode 46; D, electrode 37). The frequency range (70–115 Hz) is the same used by SIGFRIED. Red curves represent the ratio of mean power during task performance to rest. Dotted black curves represent the SD of the PSD during rest periods immediately preceding the respective task.

[21,22,27–29]. Though effective in locating cortical sites, these methods required statistical comparisons of the active and rest states after the patients performed the task. While easily accommodated in the extraoperative setting, in an awake craniotomy this time extension can be a liability. Our experience suggests that SIGFRIED locates functional regions much faster than these methods and conventional DECS.

In this preliminary study, we used classic motor and speech tasks to identify corresponding functional areas. It is important to note that stimulus presentation can be customized, so that this mapping technique is not limited to standard speech or motor paradigms. Possibilities include localization of different language sites for multilingual subjects [30], alternate motor tasks particularly pertinent to the subject (i.e., playing a musical instrument), and performance of other cognitive actions that may be more difficult to identify through standard stimulation methods such as mathematical computations and working memory tasks.

It is important to note that despite our encouraging results in two subjects, it is currently unclear whether this passive mapping

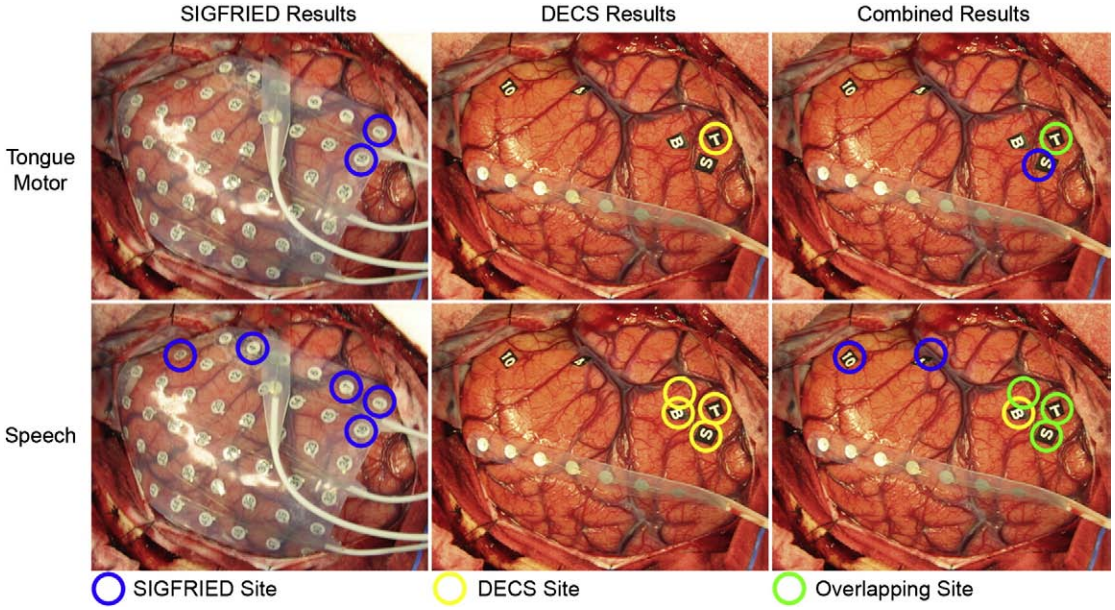

Fig. 4. Functional localization for patient A. Cortical localization of functional sites identified by SIGFRIED (left column), DECS (middle column), and both methods combined (right column) for tongue motor (top) and speech (bottom). Cortical sites are identified by blue circles when identified by SIGFRIED, and yellow circles when identified by DECS; green circles indicate common sites identified by both techniques.

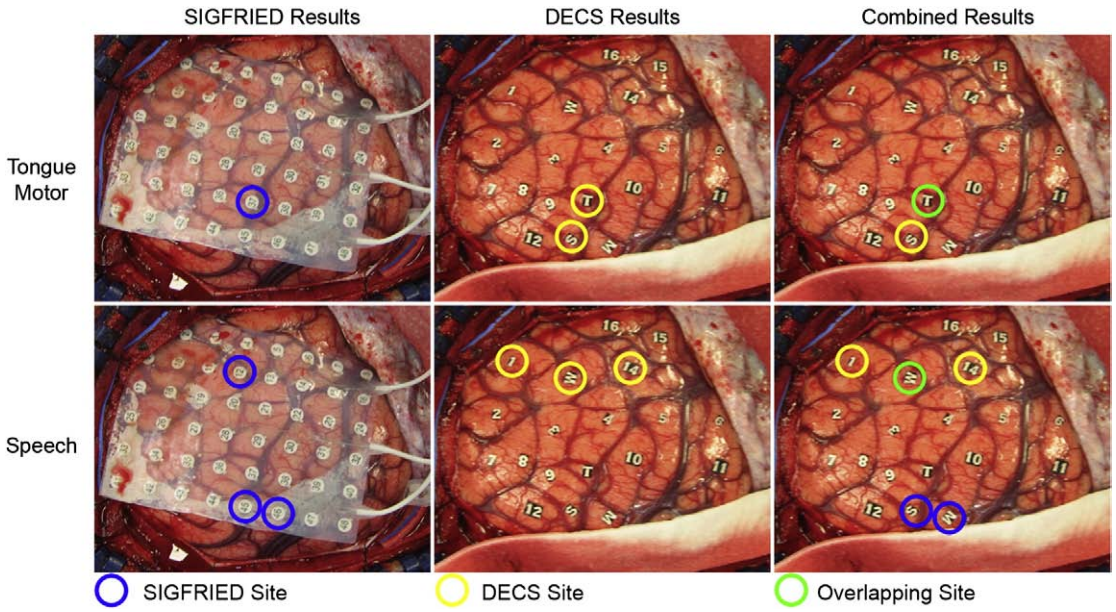

Fig. 5. Functional localization for patient B. Cortical localization of functional sites identified by SIGFRIED (left column), DECS (middle column), and both methods combined (right column) for tongue motor (top row) and speech (bottom row). Cortical sites are identified by blue circles when identified by SIGFRIED, and yellow circles when identified by DECS; green circles indicate common sites identified by both techniques.

procedure will actually reduce the risk of mapping and improve functional outcomes. Thus, future research with a larger number of patients is required to determine clinical efficacy and the associated risk profile. If the results of such research are consistent with this small case report, one could envision routinely using SIGFRIED to quickly identify relevant functional cortical areas first (i.e., motor, speech, or other processes) and then tailor stimulation to the highest-yield cortical areas subsequently. This may serve to reduce the amount of stimulation required to obtain a functional map and thereby reduce the number of afterdischarges (and potential seizures) induced by stimulation.

In addition to the intraoperative setting, alternative means for mapping cortical function exist outside of the operating room. In the surgical treatment of refractory epilepsy, or if a patient is not a good clinical candidate for awake craniotomy, a two-stage surgery may be indicated in which an ECoG grid is implanted in the first procedure to be used for functional mapping prior to any resection that may be performed in the second procedure. At this time the clinician may proceed to map a large cortical area by systematically applying bipolar stimulation between all relevant electrode pairs and observing for temporarily induced lesions, overt movements, or somatic sensations. [31] This method avoids the risk of noncompliance in the operating room attributable to poor recovery from anesthesia by allowing the patient ample time to recover and proceed with mapping at the bedside when the patient is fully awake. However, this also necessitates a longer hospital stay and exposes the patient to the risks of a second craniotomy and a mildly increased risk of infection due to the externalized wires associated with grid placement.

Alternatively, preoperative functional imaging modalities may serve a unique role in cortical mapping. Among others, the more common modalities include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) [32–34]. Conceptually these techniques share similar methodology but take advantage of the strengths of their respective technologies. These methods also have the unique advantage of being able to co-register their preoperative data with neuronavigation tools in the operating room to help guide in surgical planning. PET and MEG require specialized technology that is not commonly available, whereas fMRI is widely available and more commonly studied. Functional MRI relies on changes in the blood oxygen level-dependent (BOLD) signal, which is thought to be a measure of the hemodynamic response to local cortical activity [35]. Such an indirect measure of neuronal activation may be less precise and has been shown to vary across a number of conditions including pathology such as tumors [36]. The imprecise understanding of the neurophysiological correlation has thus far precluded fMRI from becoming a consistent and reliable means of clinical mapping [37].

SIGFRIED has been used in both brain–computer interface applications [25] and extraoperative cortical mapping [6]. It has also shown promising early results in the extraoperative setting of functional mapping prior to epilepsy surgery. A recent report on 10 patients from this population showed no false negatives and 0.46 and 1.10% false positives for hand and tongue motor tasks, respectively, when using a next-neighbor analysis [24]. In our present study, we extended these results to the noisier, challenging, and time-critical intraoperative setting and to the presence of anatomic pathology (i.e., tumors) that can distort functional regions.

In summation, SIGFRIED is a method that creates a statistical description of baseline ECoG signals and automatically detects deviations from that baseline as the subject engages in different tasks. This method can be used for rapid real-time functional mapping in the setting of an awake craniotomy. In this preliminary study, we demonstrated that this mapping can be accomplished in a practical and timely manner. Analogous to the current use of somatosensory evoked potentials in facilitating the efficiency of DECS for motor cortex, SIGFRIED may provide an adjunct modality that could be broadly used to facilitate localization of any functional site prior to DECS identification.

Acknowledgments

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Appendix A. Supplementary Data

A supplementary video associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2010.02.017.

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