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A practical procedure for real-time functional mapping of eloquent cortex using electrocorticographic signals in humans

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ABSTRACT

Functional mapping of eloquent cortex is often necessary prior to invasive brain surgery, but current techniques that derive this mapping have important limitations. In this article, we demonstrate the first comprehensive evaluation of a rapid, robust, and practical mapping system that uses passive recordings of electrocorticographic signals. This mapping procedure is based on the BCI2000 and SIGFRIED technologies that we have been developing over the past several years. In our study, we evaluated 10 patients with epilepsy from four different institutions and compared the results of our procedure with the results derived using electrical cortical stimulation (ECS) mapping. The results show that our procedure derives a functional motor cortical map in only a few minutes. They also show a substantial concurrence with the results derived using ECS mapping. Specifically, compared with ECS maps, a next-neighbor evaluation showed no false negatives, and only 0.46 and 1.10% false positives for hand and tongue maps, respectively. In summary, we demonstrate the first comprehensive evaluation of a practical and robust mapping procedure that could become a new tool for planning of invasive brain surgeries.

1. Introduction

Resective brain surgery is often performed in people with intractable epilepsy, congenital structural lesions, vascular anomalies, and neoplasms. Surgical planning of the resection procedure depends substantially on the delineation of abnormal tissue, for example, epileptic foci or tumor tissue, and on the creation of a functional map of eloquent cortex in the area close to that abnormal tissue. Traditionally, different methodologies have been used to produce this functional map: electrical cortical stimulation (ECS) [1–3], functional magnetic resonance imaging (fMRI) [4], positron emission tomography (PET) [5,6], magnetoencephalography (MEG) [7], and evoked potentials (EP) [8]. Each of these methods has problems that include morbidity, time consumption, expense, and practicality. As ECS has three-quarters of a century of historical and clinical relevance [9], and perhaps also because of its relative procedural simplicity and low cost, ECS has become the gold standard in mapping eloquent cortex. It has gained broad acceptance despite limited data to support efficacy [10] and despite several substantial issues. For example, ECS is time consuming because it requires a comprehensive search, that is, stimulation of each grid contact, while simultaneously determining the appropriate stimulation amplitude. ECS can also produce afterdischarges that may trigger seizures or even status epilepticus. This can result in substantial delays, aborted procedures, and patient morbidity. The results derived using ECS may also not be correct because: (1) stimulation may produce inhibitory responses that cannot readily be observed; (2) propagation of stimulation current is affected by the anatomy and potential after discharges, and thus variable; (3) there may be substantial procedural variability; and (4) stimulation-based mapping is based on a lesional and not a phys-

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Table 1
Comparison of the properties of ECS mapping and ECoG-based mapping

	Electrical cortical stimulation	ECoG-based passive mapping
Time consuming	Yes	No
Risk of seizure induction	Yes	No
Difficulty in observing inhib. resp.	Yes	No
Necessity for antiepileptic drugs	Yes	No
Variable prop. of stim. current	Yes	No
Procedural variability	Yes	No
Nonphysiological model	Yes	No
Patient compliance necessary	Yes	Currently yes
Proven by clinical studies	Yes	Not yet

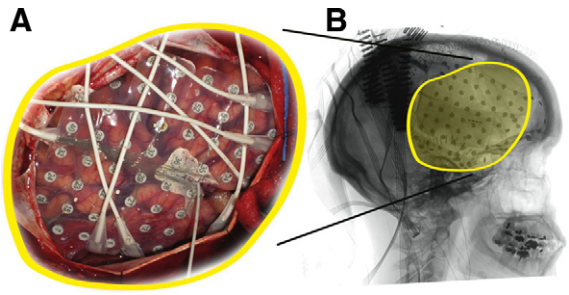

Fig. 2. Example of an implanted subdural grid in patient AMC3. (A) Subdural grid placed over frontoparietal areas. (B) Lateral radiograph indicating the position of the grid.

iological model. Finally, ECS depends on patient compliance and, thus, cannot easily be used in some patient populations (such as pediatric patients). The characteristics of ECS are summarized in Table 1 and are reviewed in [11,12]. The problems described above increase the risk to the patient and the time and cost associated with surgical planning.

Patients undergoing invasive brain surgery would benefit greatly from a mapping methodology that does not have the problems associated with existing techniques, that is, a method that is safe, can be rapidly applied, is comparatively inexpensive, is procedurally simple, and also is congruent to existing techniques (in particular to electrical stimulation). Task-related changes detected in electrocorticographic (ECoG) recordings appear to have attractive properties (see Table 1) and, thus, could provide the basis for a technique with those desirable characteristics. This approach seems particularly attractive because existing surgical protocols typically already include the placement of subdural electrodes, and because a number of recent studies have shown that ECoG activity recorded from these electrodes reflects task-related changes [13–24]. These studies showed that ECoG amplitudes, in particular, frequency bands carry substantial information about movement or language tasks. Specifically, amplitudes typically decrease in the mu (8–12 Hz) and beta (18–25 Hz) bands, whereas amplitudes usually increase in the gamma (>40 Hz) band (see Fig. 1). Furthermore, recent studies have demonstrated that such ECoG changes, in particular those in the gamma band, were in general agreement with those derived using fMRI [25] and with results determined using ECS [22–24]. However, these traditional ECoG-based analyses usually need to be optimized for each individual. Typically they are generated by signal processing experts after comprehensive post hoc analyses. Although a few recent studies have provided encouraging evidence that ECoG-based analyses could become more accessible to clinicians [26–28], a widely available and robust procedure that can be used by nonexperts is needed (See Fig. 2).

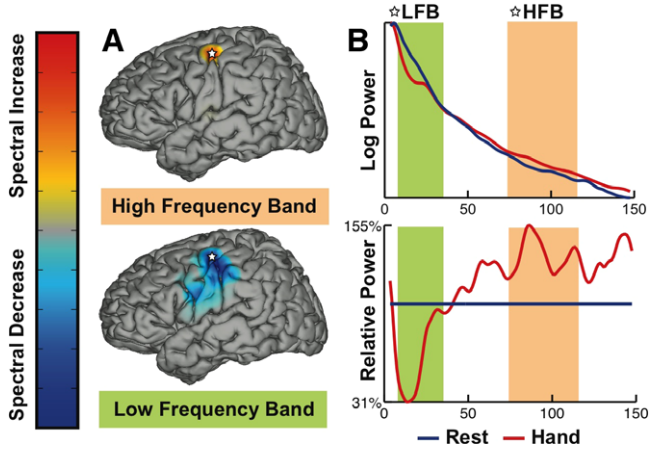

Fig. 1. Example of ECoG signal changes between the tasks of repetitively opening and closing the hand and resting. (A) Signals in the mu/beta band (5–30 Hz) decrease with the task and are spatially less specific (lower topography), whereas signals in the gamma band (70–116 Hz) increase with the task and are spatially more specific (upper topography). (B) The power spectrum on a logarithmic scale for the electrode marked with a star in the topographies illustrates the spectral decrease in the mu/beta band (marked by the green bar) and the spectral increase in the gamma band (orange bar). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

We demonstrate here a comprehensive evaluation of a robust, practical, and readily available procedure for presurgical functional mapping of eloquent cortex using subdural electrodes. This procedure is based on our BCI2000 and SIGFRIED (SIGnal modeling For Real-time Identification and Event Detection) technologies. BCI2000 is a general-purpose software platform for real-time biosignal acquisition, processing, and feedback [29,30] (http://www.bci2000.org). In collaboration with other institutions, most notably the University of Tübingen in Germany, we have been developing BCI2000 for close to 10 years. BCI2000 is currently in use by more than 350 laboratories worldwide for a variety of studies. It supports more than 15 different signal acquisition devices and can thus be readily integrated into different research or clinical environments. SIGFRIED [31,32] is a signal processing procedure implemented within BCI2000 that can detect and visualize task-related changes in real-time without prior parameterization (e.g., of frequency bands, visualization parameters, etc.) by an expert.

In this article, we demonstrate the use of the SIGFRIED/BCI2000 system for delineating cortical areas related to tongue and hand motor function in 10 patients from four institutions. The results show that our method can provide a functional map within only a few minutes and that this map is in strong congruence to that derived by ECS mapping. Furthermore, they demonstrate that our technique provides robust and practical mapping capabilities in different clinical environments.

2. Material and methods

2.1. Human subjects

A total of 10 patients (Table 2) at Albany Medical Center (Albany, NY, USA) [AMC1-5], Barnes–Jewish Hospital (St. Louis, MO, USA) [BJH1], Middleton Memorial Veterans Hospital (Madison, WI, USA) [VAH1-2], and University Medical Center Utrecht (Utrecht, The Netherlands) [UMC1-2] were implanted with subdural platinum electrode arrays (4 mm diameter, 2.3 mm exposed, 1 cm interelectrode spacing, Ad-Tech, Racine, WI, USA) for a period of 5–12 days prior to resection of a seizure focus. In each patient,

Table 2
Patient characteristics

Subject	Age	Handedness	Gender	Hemispheric dominance for language (IPA)	Full Scale IQ	Surgery hemisphere	Stimulation duration (h)	Fraction of electrodes stimulated
AMC1	19	Right	Male	N/A[a]	N/A[b]	Left	5	100% (48/48)
AMC2	61	Right	Female	Left	95	Left	5	71% (52/77)
AMC3	32	Right	Female	Left	99	Right	4	40% (24/48)
AMC4	29	Right	Male	Left	94	Right	3	100% (84/84)
AMC5	50	Right	Male	Bilateral	109	Right	2	43% (36/83)
VAH1	62	Right	Male	Left	N/A[c]	Right	1.5	70% (45/64)
VAH2	36	Right	Male	Left	N/A[d]	Right	2.5	26% (26/128)
UMC1	28	Right	Male	Left	92	Left	4.5	93% (112/120)
UMC2	27	Right	Female	Left	69	Left	7.5	69% (72/112)
BJH1	44	Left	Female	Bilateral	95	Left	1.5	88% (56/64)

[a] IPA was not administered.
[b] IQ was not tested; patient completed 12 years of education.
[c] IQ was not tested; information about education not available.
[d] IQ was not tested; patient completed 13 years of education.

the seizure focus was identified by neurologists using visual inspection, and eloquent cortex was identified over a period of 1.5–7.5 hours using ECS. For the majority of patients, this stimulation was not completed, thereby leaving 12 to 74% of the covered cortex without stimulation results. Grid locations were classified as hand or tongue function if stimulation (typically 1–4 mA) elicited or inhibited motor activity or sensation. Some of the contacts were not stimulated for different reasons: (1) They had no relevance to the surgical procedure; that is, they were sufficiently distant to any planned resection. (2) The minimum stimulation current (e.g., 4 mA) could not be reached without inducing pain. (3) Stimulation induced a seizure before any response was detected. (4) There were time constraints. (5) Stimulation induced global afterdischarges. The locations of the seizure foci and eloquent cortex were subsequently used for planning surgical resection. Location and duration of the implantation were determined solely by clinical criteria and only patients with some perirolandic coverage were included in the study. All patients gave informed consent through a protocol reviewed and approved by each of the participating institutions' review boards (see Fig. 2).

2.2. Data collection

During the monitoring period, we recorded ECoG signals at the bedside from 32 to 128 contacts of the implanted grids using different biosignal acquisition devices (Table 3). Scalp or grid electrodes were used for reference and ground. Data collection and stimulus presentation was accomplished using BCI2000 [29] software, a general-purpose system for real-time biosignal acquisition, processing and feedback. Real-time signal processing and visualization were performed using the SIGFRIED method [31,32] implemented within BCI2000.

Table 3
Signal recording properties

Subject	Channels	Sampling (Hz)	Filter (Hz)	Update rate (Hz)
AMC1	32	256	0.1	32
AMC2	32	256	0.1	32
AMC3	32	1200	0.1	30
AMC4	32	1200	0.1	30
AMC5	64	1200	0.01	15
VAH1	32	1061	3–512	35
VAH2	64	1061	3–512	35
UMC1	128	512	0.15–134.4	16
UMC2	128	512	0.15–134.4	16
BJH1	64	1200	0.1	30

2.3. Experimental protocol

We first recorded 6 minutes of baseline data during which the subject was asked to remain relaxed and to avoid any movements. Then, each subject performed alternating sequences of repetitive movements of the tongue, that is, protrusion and retraction of the tongue; movements of the hand, that is, opening and closing of the hand contralateral to the side of the grid placement; and resting. The subject was visually cued by the word "tongue" or "hand", which was presented on a computer screen (a blank screen indicated the resting period). Each task was performed for 3 seconds (15 seconds for subject UMC1) at a self-paced rate of about two repetitions per second, followed by a resting period of the same duration (Fig. 3) before the next task. One run consisted of 15 repetitions of this sequence over the course of 180 seconds. We typically recorded one initial run to familiarize the subject with the task. All analyses in this article are for one run following the initial training run. The visual display to the investigator during online operation of this run was provided as described below.

2.4. Signal analysis

To provide a basis for real-time feedback, we first used the SIGFRIED procedure [31,32] to establish a statistical model of the recorded baseline data. While the subject executed the task, we then used this procedure to identify in real-time those grid contacts that showed activity changes that were statistically different from the baseline model. In short, we used the following signal preprocessing, feature extraction, and feature selection configurations: First, the signal from each grid contact was re-referenced using a common average reference (CAR) filter [33]. Then, for each grid contact and 500-ms period, the time series ECoG signal was converted into the frequency domain using an autoregressive model [34–36] with a model order of 1/10th of the sampling rate. Frequencies between 70 and 100 Hz (10 bins at 4-Hz bandwidth) were submitted to SIGFRIED. During online processing, SIGFRIED then used the established baseline model to calculate for each grid contact the likelihood that the signal at that grid contact was statistically different from the modeled baseline signals. This likelihood was calculated every 28.27 to 66.66 ms (see Table 3).

Fig. 4 illustrates time courses of the negative log-transformed likelihood values for two locations recorded from subject VAH2. The upper trace corresponds to the location marked with a star in (See Fig. 2)Fig. 7. The bottom trace corresponds to the location marked with a rectangle. The times of cue presentation for hand movements are marked with yellow bars, and those for tongue

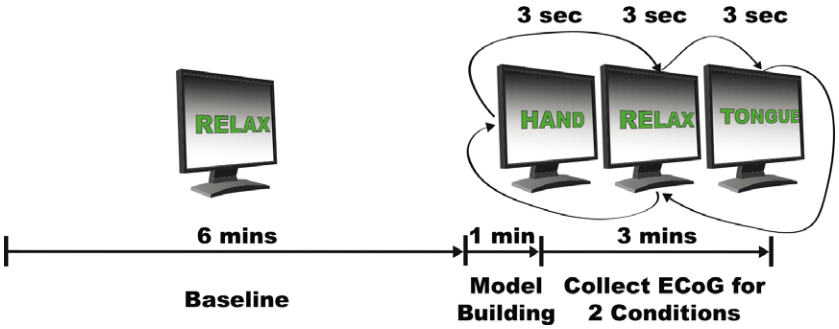

Fig. 3. SIGFRIED-based mapping procedure: After an initial 6-minute baseline period, an automated routine generates a statistical signal model for that baseline period for each electrode (this automated procedure takes less than 1 minute). The subject then alternated between hand and tongue movement tasks interspersed with rest periods.

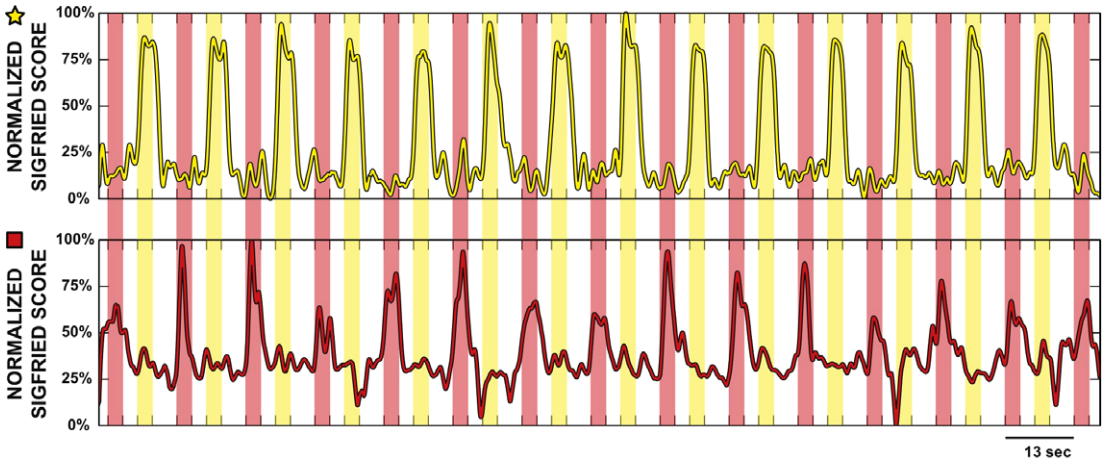

Fig. 4. Output of the SIGFRIED procedure for two locations recorded from subject VAH2. Locations for hand (top) and tongue (bottom) electrodes are each marked in Fig. 7 by a star and rectangle, respectively.

movements, with red bars. Interleaved rest periods are shown in white. The SIGFRIED trace in the upper figure detects hand movements but not tongue movements, whereas the bottom trace detects tongue but not hand movements.

Finally, for each grid contact and task, the distribution of the negative log-transformed likelihood values was further re-referenced to those values calculated during the resting period between the tasks by calculating the value of r^2, that is, the proportion of values that was accounted for by the task. This resulted in a value between 0 (not different) and 1 (very different) for each grid contact and task.

2.5. Interface to the investigator

The results from the signal analyses described above were presented to the investigator in real-time using a topographic interface (Fig. 5). The interface contained, for each task (i.e., hand or tongue), a display of the r^2 values at each location. Each display contained one

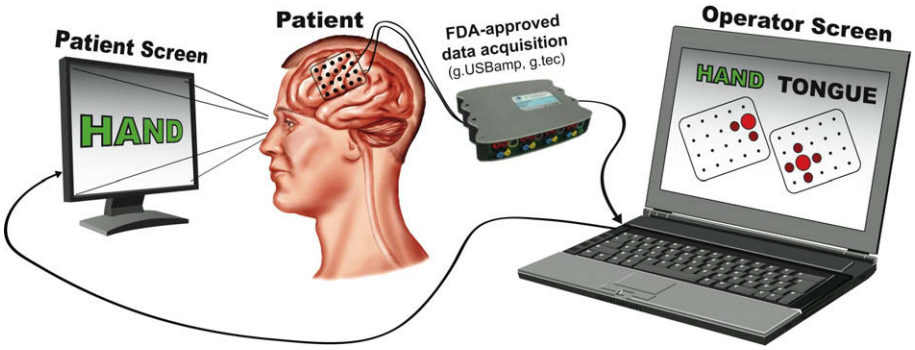

Fig. 5. Equipment setup and interface to the investigator. The subject is presented with visual cues shown on a computer monitor while electrocorticographic signals are recorded. Both the patient screen and the data acquisition device are interfaced with a laptop computer running BCI2000. BCI2000 acquires signals from the device, submits these signals in real time to the SIGFRIED method, and presents the results visually in a topographical display to the investigator.

circle at each electrode's location. The size of each circle and its tint was proportional to the r^2 value. Thus, a large red circle represented a large statistical difference between the corresponding task and rest, whereas a small black circle indicated a small statistical difference. The display corresponding to each task was autoscaled to the minimum and maximum r^2 value. Thus, no parameter (e.g., frequency range, display or detection parameters) needed to be changed by the investigator prior to or during system operation.

3. Results

3.1. Qualitative results

The following paragraphs describe the results derived using the SIGFRIED mapping procedure, and qualitatively and quantitatively compare the results with those obtained with ECS mapping.

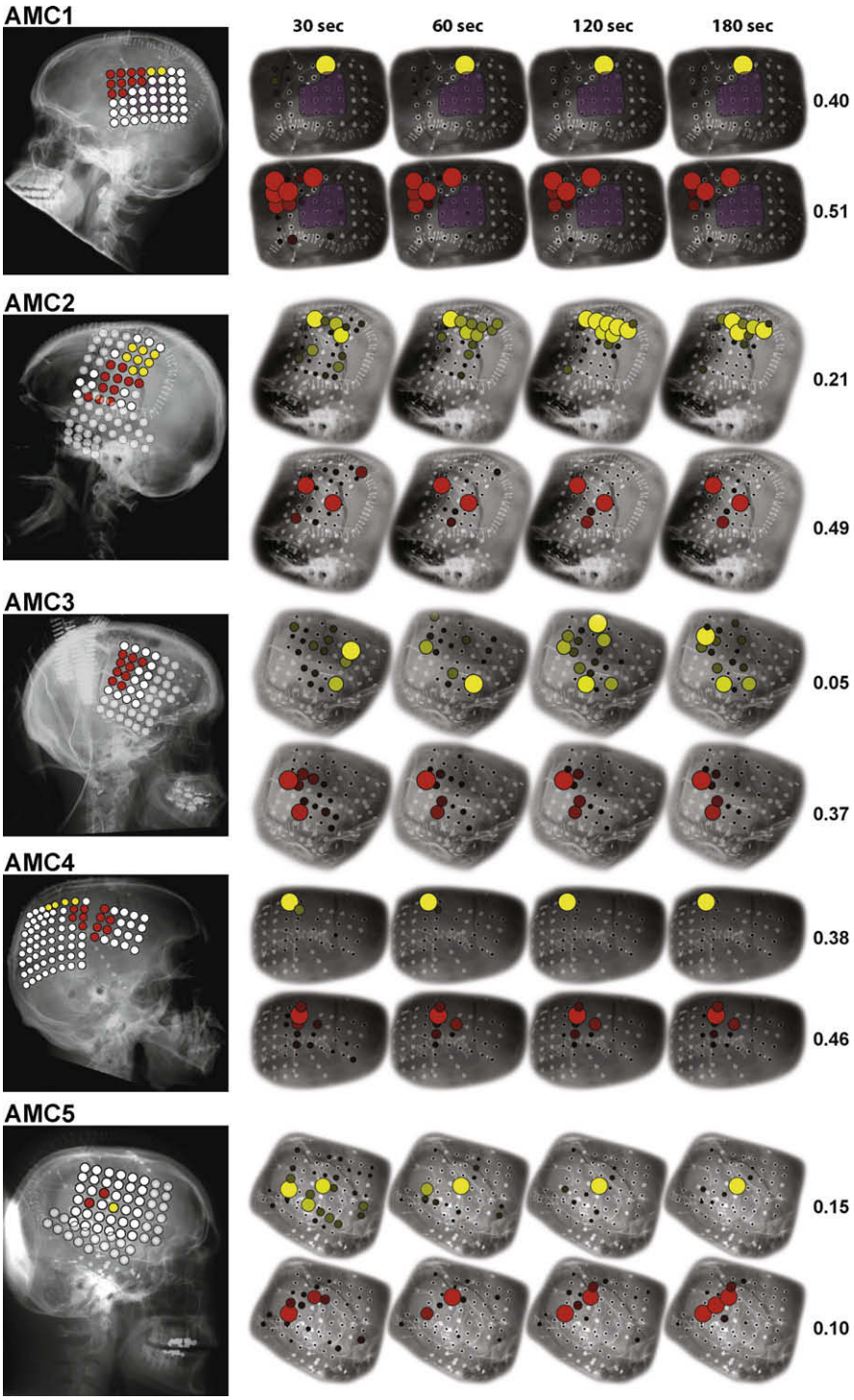

Fig. 6. Results of electrical cortical stimulation (left) and passive functional mapping using SIGFRIED (right) for subjects AMC1 to AMC5. Lateral radiographs (left) show the results of electrical cortical stimulation for hand (yellow) and tongue (red) and no response to hand or tongue (white). Transparent circles indicate no stimulation. Detailed lateral radiographs (right) show the result of passive functional mapping using SIGFRIED after 30, 60, 120, and 180 seconds for hand (yellow) and tongue (red). The number indicates the final maximum r^2 between the stimulus and the SIGFRIED response (0 to 1). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

The main results of this article are illustrated for all subjects in Figs. 6 and 7, and in Supplementary Videos 1 and 2. In each figure, the lateral radiographs (all subjects except UMC1 and UMC2) or computer tomography (CT) images (UMC1 and UMC2) on the left show grid contacts marked by colored circles. Contacts that were stimulated and identified as eloquent cortex associated with hand function are shown in yellow, those associated with tongue function are shown in red, and those associated with neither hand nor tongue function are shown in white. Semitransparent white circles indicate locations that were not stimulated.

The four detailed lateral radiographs/CT images on the right show the results of the SIGFRIED mapping procedure derived after

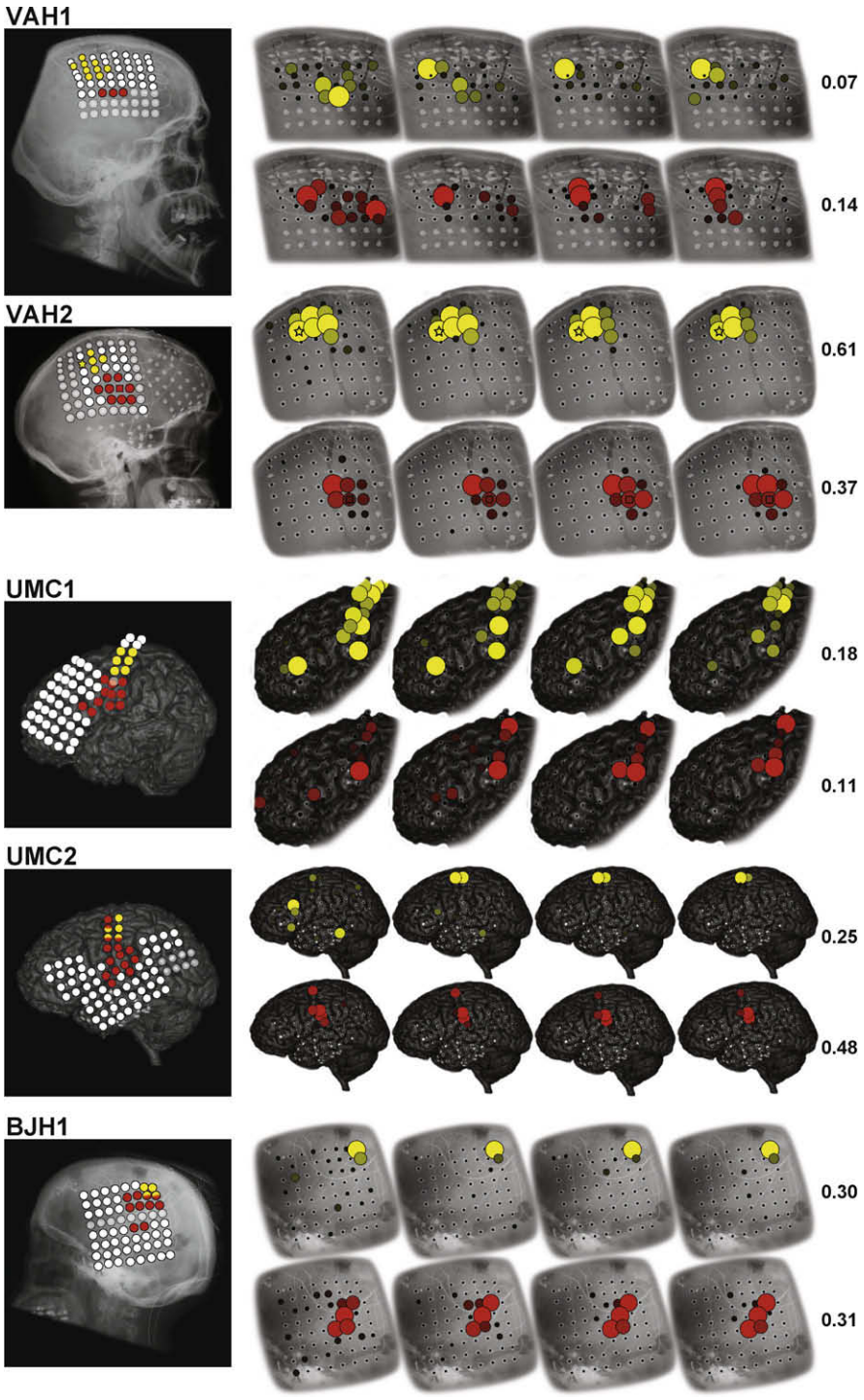

Fig. 7. Results of electrical cortical stimulation (left) and passive functional mapping using SIGFRIED (right) for subjects VAH1, VAH2, UMC1, UMC2, and BJH1. Lateral radiographs or computer tomographic renderings (left) show the results of electrical cortical stimulation for hand (yellow) and tongue (red) and no response to hand or tongue (white). Transparent circles indicate no stimulation. Detailed lateral radiographs (right) show the result of passive functional mapping using SIGFRIED after 30, 60, 120, and 180 seconds for hand (yellow) and tongue (red). The number indicates the final maximum r^2 between the stimulus and the SIGFRIED response (0 to 1). The real-time SIGFRIED traces in Fig. 4 are for the locations marked by a yellow star and red rectangle in subject VAH2, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

Table 4
Highest squared correlation (r^2) between the task and the SIGFRIED output, and minimum Bayesian error between the results of electrical cortical stimulation and SIGFRIED mapping

Subject	Hand			Tongue		
	r^2	False positive	False negative	r^2	False positive	False negative
AMC1	0.40	0.00%	0.00%	0.51	12.50%	0.00%
AMC2	0.21	4.17%	4.17%	0.49	12.50%	12.50%
AMC3	N/A[a]	N/A[a]	N/A[a]	0.37	16.67%	11.11%
AMC4	0.38	0.00%	0.00%	0.46	4.00%	12.00%
AMC5	0.15	0.00%	0.00%	0.10	0.00%	3.70%
VAH1	0.07	10.35%	0.00%	0.14	10.35%	0.00%
VAH2	0.61	3.57%	0.00%	0.37	3.57%	0.00%
UMC1	0.18	3.33%	1.67%	0.11	10.00%	1.67%
UMC2	0.25	3.75%	2.50%	0.48	10.00%	1.25%
BJH1	0.30	3.57%	1.79%	0.31	10.71%	0.00%
Average	0.26	3.19%	1.12%	0.33	9.03%	4.22%

[a] Electrical cortical stimulation resulted in no hand hits for subject AMC3.

Table 5
Highest squared correlation (r^2) between the task and the SIGFRIED output, and minimum Bayesian error between the results of electrical cortical stimulation and SIGFRIED mapping in a next-neighbor comparison

Subject	Hand			Tongue		
	r^2	False positive	False negative	r^2	False positive	False negative
AMC1	0.40	0.00%	0.00%	0.51	0.00%	0.00%
AMC2	0.21	4.17%	0.00%	0.49	4.17%	0.00%
AMC3	N/A[a]	N/A[a]	N/A[a]	0.37	5.56%	0.00%
AMC4	0.38	0.00%	0.00%	0.46	0.00%	0.00%
AMC5	0.15	0.00%	0.00%	0.10	0.00%	0.00%
VAH1	0.07	0.00%	0.00%	0.14	0.00%	0.00%
VAH2	0.61	0.00%	0.00%	0.37	0.00%	0.00%
UMC1	0.18	0.00%	0.00%	0.11	0.00%	0.00%
UMC2	0.25	0.00%	0.00%	0.48	1.25%	0.00%
BJH1	0.30	0.00%	0.00%	0.31	0.00%	0.00%
Average	0.26	0.46%	0.00%	0.33	1.10%	0.00%

[a] Electrical cortical stimulation resulted in no hand hits for subject AMC3.

30, 60, 120, and 180 seconds. Similar to the ECS results shown on the very left, yellow circles indicate the results for the hand task, and red circles indicate the results for the tongue task. Locations that were excluded (e.g., due to broken connectors) or not recorded (e.g., due to limitation in the number of channels) are left blank. The final maximum r^2 (i.e., the value of r^2 of the largest circle in each figure) after 180 seconds is noted on the right for hand (range: 0.05–0.61) and tongue (range: 0.10–0.51).

3.2. Quantitative results

The results in Figs. 6 and 7 substantially agree with those derived using electrical stimulation. In addition, we assessed these results using two quantitative comparisons. For both comparisons of tongue and hand, the r^2 values at each location were classified as eloquent or non-eloquent with a threshold that was derived using minimum Bayesian error [37].

The first comparison in Table 4 provides a quantitative analysis for the 18 to 77 contacts that were both stimulated by ECS and mapped with SIGFRIED. This comparison was done independently for hand and tongue and resulted in a correct or incorrect match between ECS and SIGFRIED at each location. The incorrect results were further classified into false positives, that is, contacts identified by SIGFRIED but not by ECS, and false negatives, that is, contacts identified by ECS but not by SIGFRIED. Table 4 shows that there were more false positives than false negatives. For three subjects (AMC1, VAH1 and VAH2), no false negatives for hand and tongue were identified. We hypothesized that most of the incorrect results would have been correct if they had been derived for a next-neighbor. Table 5 shows the results of the corresponding analysis. Although this analysis effectively corresponds to a reduction in the resolution of the mapping, this procedure resulted in no false negatives, and only in 0.46 and 1.10% false positives for hand and tongue maps, respectively.

4. Discussion

We provide the first comprehensive demonstration of a functional mapping procedure that is rapid, practical, robust, and accurate in localizing primary motor cortex. In our evaluation of 10 patients from four institutions, we found that the SIGFRIED procedure identifies at least the same contacts or their immediate neighbors compared with ECS mapping.

These results may have important implications for functional localization prior to invasive brain surgery. Our method can be used with little training and can be readily implemented in the typical clinical environment. In fact, our system is currently in evaluation by a number of epilepsy centers in the United States and Europe. Thus, we believe that the SIGFRIED/BCI2000 system has the potential for widespread adoption in a large number of centers worldwide. At the same time, this new mapping platform has opened up several important research questions: Which tasks are best suited to elicit appropriate responses for different classes of anatomical areas? What are the situations or populations (e.g., children) for which this method provides the maximum benefit? What is the efficacy of the SIGFRIED method for other brain functions, in particular, for mapping expressive and receptive language? (Ongoing work in our laboratory is providing encouraging

evidence in this regard.) It is at present also unclear how this method will be integrated into the clinical workflow. Despite the strong congruence of the SIGFRIED-based results with ECS-based results, it is likely premature to replace ECS mapping with SIGFRIED-based mapping. Rather, it seems more appropriate to optimize ECS mapping based on the results of prior SIGFRIED mapping.

Like the recent study by Miller et al. [23], our study demonstrates considerable variance in the somatotopy across subjects and coherence with the ECS mapping results. Both location and area identified as eloquent cortex vary among subjects. Although for Miller et al. it was not clear whether this was due to subject variability or expert variability in performing the ECS, our study shows that a next-neighbor analysis achieves almost perfect coherence with the ECS mapping results. This suggests that most of the variance is due to expert variability.

Crone et al. [14] reported that not all subjects displayed changes in the gamma band. This contrasts with the results of this study, which showed adequate task-related changes of gamma amplitudes (which were the basis for the SIGFRIED calculations) in all 10 subjects. It is possible that this is due to a difference in hardware, processing, or motor tasks. For example, our own experience, and also results from a previous study [15], suggests that more complex tasks (such as the Rubic's cube manipulation task in Supplementary Videos 1 and 2) increase the amplitude of the gamma changes.

The SIGFRIED results were generally in substantial agreement with those derived using electrical stimulation, but there were some differences. These differences could be attributed to several factors that include expert variability in ECS mapping or ECS's variable current spread, low statistical significance, or the characteristics of the subject's task. Cortex at remote locations may be activated due to current spread, resulting in a site that is registered by ECS and not by SIGFRIED. Conversely, SIGFRIED may falsely register sites with low statistical significance. For example, consider the map for hand function in subject AMC3 (shown in Fig. 6). This subject's grid did not have hand coverage; that is, ECS mapping did not detect hand function in any electrode. The SIGFRIED map highlights several sites, although the maximum r^2 value (0.05) was very low. Thus, the magnitude of the maximum r^2 value provides and index of confidence in a particular map. Future versions of the software could even calculate such a confidence index (i.e., a p value) explicitly. The factor that may have the largest influence on the differences between the ECS and SIGFRIED maps may be the nature of the subject's task. In one extreme, this task would be very simple, and require only very limited areas of cortex for its execution. In this case, SIGFRIED would register only very few electrodes or none at all. In the other extreme, the subject's task would be difficult and require engagement of different cortical facilities. Thus, the use of this task would result in activation of more widespread areas of cortex, and consequently, SIGFRIED would detect changes in more electrodes. As described above, recent experiments suggest that the use of more complex visuomotor tasks results in even more robust maps. In sum, the optimal tasks for mapping motor and other cortices using the SIGFRIED method are currently unknown. However, the rapidity of our method facilitates the use of several tasks that engage the desired cortical area in different ways.

SIGFRIED mapping overcomes many problems associated with ECS. It is also based on a different principle. Although ECS is based on a lesional model [38], SIGFRIED is based on task-related changes in ECoG signals. The clinical impact of this difference is currently unclear. It is thought that the lesional model used with ECS closely resembles the effect of surgical resection, in that it allows the identification of those areas that are critical for a particular function. In contrast, SIGFRIED detects those areas that change their activity with a particular task. It may not detect areas that do not change their activity but are critical for a particular function, or may detect areas that change their activity but are not critical. At the same time, ECS clearly has problems of accuracy itself, for example, because there is no defined standard for ECS mapping, because there are practical (in particular, time) constraints for using ECS, and because the resolution of ECS is limited due to current spread and the need for bipolar stimulation. In summary, at this early stage of clinical validation, replacing ECS with the SIGFRIED/BCI2000 system is not warranted. Nevertheless, despite its potential limitations, there may already be distinct advantages over ECS mapping.

The ECS protocol labels each contact with the eloquent function that is elicited or inhibited as the contact is stimulated. Finding eloquent function at a low threshold terminates the protocol for this contact, assuming that each type of eloquent function is spatially contiguous, as is suggested by the motor homunculus model [39]. Recent fMRI [40] and ECS [10] studies, however, show a more complex and spatially noncontiguous somatotopy. SIGFRIED mapping could establish a comparable somatotopy by exploring different tasks, for example, a dedicated motor/sensory evaluation for each finger. This could allow more detailed surgical planning and thus benefit the outcome of the resection procedure. However, the lack of a verifiable gold standard makes it difficult to assess the quality of such a more detailed somatotopy. Only surgical outcome can provide a detailed assessment on whether a more detailed somatotopy may be beneficial.

Studies have shown task-related changes associated with ipsilateral movements in the low-frequency band [41–48]. The implications of resecting cortical areas associated with these ipsilateral movements have not been defined, mainly because ECS is not able to elicit ipsilateral limb movement within the conventional stimulation thresholds [49,50]. SIGFRIED mapping could facilitate such studies by exploring ipsilateral tasks.

An initial application of the SIGFRIED/BCI2000 system is shown here, but there are several ways in which this system can be further improved. As a first example of the potential for improvement, we observed a noticeable delay between stimulus onset and the patient's response even when there was good compliance of the subject. Crone et al. also reported such delays, and estimated them to be in the 300–400 ms range for simple visually cued hand movements and tongue protrusions [14]. Our results show similar delays (see Fig. 4). Because the total duration of each stimulus was only 3 seconds (15 seconds for subject UMC1), a significant fraction of the signals were thus effectively assigned to the incorrect task category. In more recent experiments, we have begun to alert the subject to the change in condition by presenting an auditory stimulus, and we suspend data analysis for 1 second. In the end, it may be possible to partially or even completely eliminate this need for patient compliance, which is currently an issue for all mapping techniques. For example, for motor tasks it would be relatively straightforward to use motion sensors, such as a data glove, motion capture device, or EMG electrodes, and simply to correlate SIGFRIED values with the detected motion rather than with the stimulus. For sensory input, it would be possible to use programmable tactile stimulators and earphones. Thus, such approaches may fully remove the requirement for patient compliance and facilitate mapping in pediatric environments where patient compliance is either impossible (e.g., with infants) or hard to obtain (e.g., with young children). As another example of a potential improvement, it may be possible to use SIGFRIED mapping intraoperatively. This could replace the two surgeries that are currently necessary with one surgery that encompasses grid placement, mapping of eloquent cortex, and resection. In particular, in patients who do not require longer monitoring periods (e.g., patients with tumor), this would significantly decrease risks to the patient and costs of hospitalization.

In conclusion, we have described the SIGFRIED/BCI2000 system as a practical functional mapping procedure. This system is readily

available at no cost for research and educational purposes at www.bci2000.org, and there is substantial documentation on its theory [29–32] and use (doc.bci2000.org). BCI2000 currently supports signal acquisition from 15 different devices, and more are continually added. This should facilitate integration into existing clinical environments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2009.04.001.

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