Passive functional mapping guides electrical cortical stimulation for efficient determination of eloquent cortex in epilepsy patients

Conference Paper *in* Conference proceedings: ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference · July 2017

DOI: 10.1109/EMBC.2017.8037773

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Passive functional mapping guides electrical cortical stimulation for efficient determination of eloquent cortex in epilepsy patients*

Robert Prueckl, Christoph Kapeller, Johannes Gruenwald, Hiroshi Ogawa, Kyousuke Kamada, Milena Korostenskaja, James Swift, Josef Scharinger, Guenter Edlinger, and Christoph Guger

Abstract — **Electrical cortical stimulation (ECS) is often used in presurgical evaluation procedures for patients suffering from pharmacoresistant epilepsy. Real-time functional mapping (RTFM) is an alternative brain mapping methodology that can accompany traditional functional mapping approaches like ECS. In this paper, we present a combined RTFM/ECS system that aims to exploit the common ground and the advantages of the two procedures for improved time/effort effectiveness, patients' experience and safety. Using the RTFM and ECS data from four patients who suffer epilepsy, we demonstrate that the RTFM-guided ECS procedure hypothetically reduces the number of electrical stimulations necessary for eloquent cortex detection by 40%.**

I. Introduction

Epilepsy is defined as a brain disorder characterized by recurrent seizures. A seizure is caused by "abnormal excessive or synchronous neuronal activity in the brain" [1]. In many cases, the quality of life of patients is severely reduced by seizures [2].

Anti-epileptic drugs allow seizure control in 70-80% of patients. The remaining 20-30% are eligible for surgical intervention, in which the seizure onset zone is resected [3], [4]. The seizure onset zone is most commonly identified by non-invasive or invasive techniques [5]. The identification of the functionally significant cortex, the eloquent cortex, surrounding the seizure onset zone, is important for predictable surgical outcome and for retaining important body functions. Different procedures based on observational and inhibition/activation techniques are available [6].

The underlying principle of electrical cortical stimulation (ECS), which belongs to the latter group, is the stimulation of brain tissue with electric current via subdural electrodes implanted in the brain of the patient. It is often part of presurgical evaluation to identify eloquent cortex [7]. Most prominent areas that can be mapped via ECS are those related to motor, sensory, language-related, visual, and auditory functions [8]. During stimulation the physicians document the patient's reactions, which are commonly manifest as activation or inactivation of muscles, sensations, or other functions [7].

In our previous work, we introduced the RTFM system *cortiQ* which can be used for mapping the eloquent cortex using the same electrodes that are used for ECS [9]. Here, we present the advanced version of this system, which aims to exploit the synergies of RTFM and ECS by integration of an electrical stimulator and a channel-switching unit.

We demonstrate the advantages of the system by evaluating data of four patients who suffer from epilepsy. We focus on the potential reduction of necessary stimulations, leading to (1) reduction in time/effort involved in performing ECS, (2) alleviated risk of seizures, and (3) increased patients' comfort.

II. System Architecture

A. Hardware

The hardware components of the presented system are a *g.HIamp* biosignal amplifier, a *g.Estim* cortical stimulator, and a *g.Eswitch* (channel-)switching unit (all from *g.tec medical engineering GmbH*, Austria). All devices are controlled via USB. As shown in Fig. 1 the electrodes are connected to headboxes via medical safety connectors and are then routed into the switching unit. Per default, the switching unit routes all channels directly to the amplifier for acquisition. Optionally, it provides a path to a clinical ECoG monitoring system. The amplifier can record up to 256 channels and allows for a sampling rate of 1200 Hz. It digitizes the data to 24-bit fixed-point numbers and sends them to the recording computer.

The software of the switching unit allows the selection of two channels for stimulation. Once the stimulator sends a trigger signal, the switching unit disconnects the selected channels from the amplifier and connects them to the stimulation input. In this way, the stimulus cannot damage the amplifier while the acquisition from the remaining channels continues.

The stimulator delivers constant-current rectangular electrical pulses with tunable polarity, length and amplitude. The maximum output amplitude is 15 mA, the length of a stimulation phase is up to 1 ms and the pulse rate is 1-500 Hz. The calculation of the charge density, which depends on the electrode surface, is a novel safety feature implemented in the system. It provides an essential check for dense electrode arrays with small exposure and ensures that the charge density is held within a safe range. Furthermore, the system warns the operator about stimulation settings, that are potentially unsafe [10].

*This work was supported by ENIAC Joint Undertaking Project DeNeCoR (No. 324257)

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Preprint submitted to 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Received February 3, 2017.

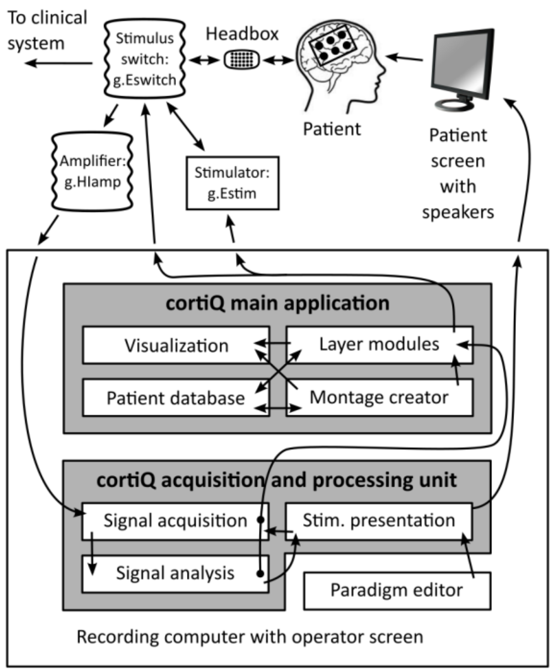

Fig. 1. Architecture of the presented system.

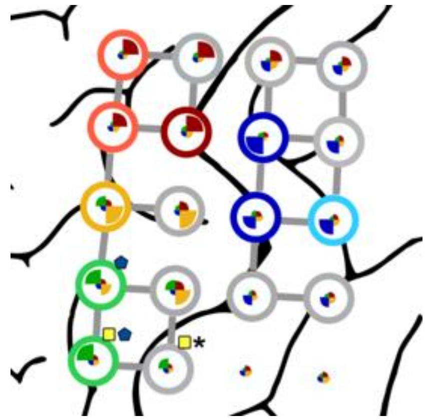

Fig. 2. Visualization of the results in the main application for a 20-channel electrode grid. The pie charts show the results of four RTFM tasks in different colors. The outer rings denote the color-coded categories of an ECS mapping. The grey lines between the electrodes represent stimulation events. The yellow square, the blue pentagon, and the asterisk represent manual annotations (e.g. data quality).

B. Software

The software developed previously for *cortiQ* [9] was adapted to integrate the new ECS feature in the new version. In the *Montage Creator* module, information about the exposed surface area of the electrodes for calculating the charge density limits was included. Furthermore, functionality for quick-connector electrodes was added. These connectors allow direct attachment of the whole electrode grid at once instead of having to plug in the medical safety connectors for each channel individually.

The user interface of the main application is structured in layers, where each of them represents a different mapping modality. All layers rely on the layout of the electrode montage for their visualization of data and results.

In the *raw-data layer*, interictal baseline data from the resting patient can be recorded. These data are processed through a signal quality check, which detects artifacts and assists in the exclusion of the contaminated channels to prevent the corruption of results.

In the *annotation layer*, the signal quality, seizure onset zone, and other valuable information can be added.

The *RTFM layer* represents the functionality described in [9]. The results of each individual RTFM run can be used to guide the ECS mapping. The ultimate goal is, to perform the mapping by stimulating only those electrodes that are suggested by RTFM.

In the *ECS layer*, two electrodes for stimulation can be selected from the montage. The stimulation amplitude can be adjusted. Stimulation is started via a mouse click and the hardware components ensure correct routing of the stimulus. After stimulation and observation of the physiological response of the patient, a category can be assigned to the tested electrodes. This information is stored along with the stimulation parameters.

Fig. 2 illustrates how the results are presented in the user interface of the main application. The visualization can be configured either to integrate as much information as possible (like in Fig. 2), or to present it more selectively, e.g., to only display the results of a single RTFM task.

The software also supports comparison of ECS and RTFM results with respect to different categories. After identifying the relations between ECS and RTFM categories, the software computes sensitivity and specificity values, thus allowing quantitative result evaluation [11]. All acquisition and analysis data are stored together in a patient database.

III. METHODS

With the proposed approach described above, we aim to reduce the number of stimulations necessary to reveal all areas of the cortex that belong to the functional area to be identified. To asses the effectiveness of the proposed method, we employ data from mapping sessions based on ECS only. Those sessions were conducted with four epilepsy patients from Asahikawa Medical University, Asahikawa, Japan and Florida Hospital for Children, Orlando, FL, USA, who underwent ECS and RTFM mapping for preoperative evaluations. ECS mapping was performed according to the clinical procedures without any prior information from RTFM.

The study was approved by the institutional review boards of the aforementioned institutions and written informed consent was obtained from the patients prior the beginning of the study.

For quantitative analysis, we establish a mathematical framework that operates on two sets, the set of implanted electrodes $\mathcal{E}$ and ECS stimulation pairs $\mathcal{S}$. As all ECS mappings in this study follow a bipolar stimulation protocol, it is thus illustrative that any stimulation pair $s \in \mathcal{S}$ refers to one electrode tuple, denoted by $(s.e_1, s.e_2) \in \mathcal{E} \times \mathcal{E}$. Since we need to cross-reference between these two domains, we define mappings from stimulation pairs to electrodes ($\mathrm{Elec}(S) \subseteq \mathcal{E}$ with $S \subseteq \mathcal{S}$) and vice versa ($\mathrm{StP}(E) \subseteq \mathcal{S}$ with $E \subseteq \mathcal{E}$) as follows:

$$\mathrm{Elec}(S) \coloneqq \bigcup_{s \in S} \{s.e_1, s.e_2\} \quad (1)$$

$$\mathrm{StP}(E) \coloneqq \bigcup_{e \in E} \{s \mid s \in \mathcal{S} \wedge (s.e_1 = e \vee s.e_2 = e)\}. \quad (2)$$

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It should be noted that these two mappings are in general not inverse to each other. From the results of the ECS procedure, we identified *relevant* stimulation pairs $S_{\mathrm{rel}} \subseteq \mathcal{S}$ that elicited a functional response according to the respective task. The corresponding electrodes are determined by

$$E_{\mathrm{GT}} = \mathrm{Elec}(S_{\mathrm{rel}}) \tag{3}$$

and serve as a ground truth (GT) here. In the context of RTFM, the tasks related to sensorimotor, face sensorimotor, and receptive language functions are denoted by T_1, T_2, and T_3, respectively. Electrodes that showed significant activation [11] are referred to as E_{T_1}, E_{T_2}, and E_{T_3}, respectively. We can merge them into the set of overall active electrodes via

$$E_{\mathrm{act}} = \{E_{T_1}, E_{T_2}, E_{T_3}\}. \tag{4}$$

Next, all stimulation pairs that contain at least one electrode with significant activation during the RTFM tasks are covered by the set of *suggested* stimulation pairs:

$$S_{\mathrm{sugg}} = \mathrm{StP}(E_{\mathrm{act}}) \tag{5}$$

In order to relate this to the ground truth, the respective suggested *electrodes* are given by

$$E_{\mathrm{sugg}} = \mathrm{Elec}(S_{\mathrm{sugg}}). \tag{6}$$

For the purpose of quantitative performance assessment, the number of stimulations involved to reveal E_{GT} is a suitable figure of merit. Clearly, $|S_{\mathrm{sugg}}|$ is the number of stimulations necessary to reveal E_{act} as suggested by RTFM. It can happen, however, that some electrodes identified by ECS are missed, which can be expressed as $E_{\mathrm{miss}} = E_{\mathrm{GT}} \setminus E_{\mathrm{sugg}}$. The amount of stimulations needed to reveal these electrodes can be estimated by $|S_{\mathrm{miss}}| \approx |E_{\mathrm{miss}}| \cdot k$, with $k = |\mathcal{S}|/|\mathrm{Elec}(\mathcal{S})|$ being the average number of stimulations necessary to reveal an electrode. Furthermore, it is possible that some electrodes denoted by the set $E_{\mathrm{nostim}} \subseteq E_{\mathrm{act}}$ are located where no stimulation took place, i.e., $\mathrm{StP}(E_{\mathrm{nostim}}) = \emptyset$. This means that the effort to identify these electrodes is not covered by $|S_{\mathrm{sugg}}|$. It must thus be estimated. According to the method mentioned above, this yields $|S_{\mathrm{nostim}}| \approx |E_{\mathrm{nostim}}| \cdot k$.

Finally, the cost function which estimates the number of necessary stimulations to reveal E_{GT} based on a suggestion E_{sugg} is

$$\hat{C}(E_{\mathrm{sugg}}) = |S_{\mathrm{sugg}}| + (|E_{\mathrm{miss}}| + |E_{\mathrm{nostim}}|) \cdot k\ . \tag{7}$$

IV. Results

The patients had electrode coverage of the assumed sensorimotor and auditory cortices. On average, 123.5 electrodes were implanted in each patient. Table I shows results of the ECS stimulation sessions. On average, 52 electrode pairs were stimulated, where on average 18.8 electrodes relate to either hand sensory, hand motor, face sensory, face motor, or language-related functions. Consequently, 15.2% of the electrodes were assigned to a category other than ‘no response’.

Language area was identified only for patient 1, in whom the stimulation of two electrodes caused a change of accent. The face sensorimotor area could not be found in patient 3. This patient developed a seizure during ECS, leading to termination of the mapping session.

TABLE I. Initial ECS mapping.

P	IE	SP	RE
1	186	77	35
2	126	46	18
3	64	32	8
4	118	53	14
Average	123.5	52	18.8 15.2%

Patient (P), no. of implanted electrodes (IE), no. of stimulation pairs (SP), no. of relevant electrodes (RE)

During RTFM sessions, all patients performed a hand motor task, a tongue movement task, a kissing task, and listened to spoken words. All patients except patient 1 additionally performed a hand sensory task. As can be seen from Table II, RTFM delivered on average 28 electrodes with significant activation (23% of all electrodes). In all patients, all tasks yielded electrodes with significant activation.

Based on the information described above, it is possible to hypothesize that the number of required (*effective*) ECS stimulations could have been reduced to 31.3 electrodes on average instead of 52, which represents only 60.2% of the ECS stimulations performed without prior knowledge of RTFM. On average, 1.5 electrodes (8%) that were assigned to a category during initial ECS mapping were missed per patient. For two patients, no electrodes were missed at all. All electrodes that were not detected fall into the face motor/sensory category.

TABLE II. ECS mapping guided by RTFM results.

P	RR	RS	ES	ME	SOG	C
1	3	65	56	2	$p < 0.001$	58.6
2	1	13	35	4	$p = 0.018$	43.3
3	1	11	8	0	$p < 0.001$	8.0
4	1	23	26	0	$p < 0.001$	25.2
Average	1.5	28 23%	31.3 60.2%	1.5 8%	N/A	N/A

Patient (P), no. of RTFM runs (RR), no. of electrodes suggested by RTFM (RS), no. of effective (hypothetically required) stimulations (ES), no. of missed electrodes (ME), significance of guidance (SOG), result of the cost function defined in Eq. 7 (C)

The mapping guided by RTFM results significantly improves the efficacy of the ECS procedure as opposed to random guidance (see column SOG in Table II). The p-values were derived from a 10,000-fold bootstrapping procedure applied on $\hat{C}(E_{\mathrm{sugg}})$ in which $E_{T_1}, E_{T_2}, E_{T_3}$ were randomly chosen. The number of suggested electrodes was held constant for each task to imitate random RTFM results. The results of the cost function defined in Eq. 7 for the RTFM suggestions of the patients are listed in column C.

V. Discussion

With the presented system, the objective is to reduce the number of currently used ECS stimulations, while maintaining the percentage of identified electrodes covering eloquent cortex. Looking at the results from ECS without guidance, on average 52 stimulations per patient were necessary to reveal targeted cortical functions, which on average made up only 15.2% of the covered cortex. To avoid mapping sessions that are exhausting for the patient and time/effort consuming for the medical professional, our approach is to start the procedure with RTFM to generate a guideline map for subsequent ECS. Compared to ECS, the RTFM is more time/effort effective and tolerable, as it is not associated with involuntary movements, uncomfortable sensations, pain, or seizures often caused by ECS. We showed that in RTFM-guided ECS sessions, the number of stimulations could be reduced by up to 40%. This considerable reduction might become highly relevant in the near future, since there is a growing tendency to use electrode grids with higher density and increased channel count. As an additional feature, the proposed system conveniently ensures restriction to safe stimulation limits. It also features a signal quality check that alleviates the effort of signal plausibility assessment and the consequences therein. Furthermore, RTFM ensures the availability of mapping results independently from the presence of ECS results, for example in case of ECS being intolerable for the patient.

For patient 1, the two electrodes not detected by RTFM were classified as 'mouth motor' in ECS. The slight difference to 'lips' as tested with RTFM could explain this issue. For patient 2, the electrodes for 'tongue movement', as suggested by RTFM, were not stimulated. Therefore, no definite conclusion about the value of the suggestion can be drawn. ECS classified four electrodes superior to the 'tongue' area suggestion that were not covered by the RTFM result as part of 'motor mouth/lip/face'. According to the homunculus, the tongue is represented inferior to the lip area. So, both results might be correct, in which case the reason for this problem would be the imprecise assignment of relations from ECS to RTFM categories. This discrepancy implicates a high cost (43.3 stimulations), which is nearly as high as in case of the ECS-only session (46 stimulations). Therefore, the improvement for patient 2 is smaller, compared to the other patients.

For patients 2 to 4, ECS did not identify the primary auditory cortex. In contrast to that, RTFM yielded electrodes with significant activation. An explanation could be the fact that mapping auditory areas with ECS is more difficult compared to sensorimotor cortex. In general, our results vary depending on the consistency of the ECS/RTFM category assignment and the choice of the tasks. It is difficult or even impossible to design RTFM mapping tasks that perfectly overlap with the results of ECS stimulation (and vice versa). We argue, however, that this gap can be closed at the best, if mapping based on ECS and RTFM is performed within the same environment and the same session by the same person.

An RTFM result is supposed to represent cortical activation elicited by the respective functional task. It is beneficial when the task is well designed and the activation is broad and strong enough to excite all corresponding areas of the cortex. It is evident that proper task design is fundamental for a good quality of RTFM results. For example, a task targeting lip motor function will obviously not activate cortical areas corresponding to tongue motor function. Consequently, careful design of RTFM tasks and description of expected results is of vital importance for ensuring a proper guidance. On the other hand, the ECS studies might also need further guidelines to be able to map cortical areas accommodating higher functions.

The main limitation of the presented study is the incompleteness of the datasets and stimulation coverage. As an implication, for suggested electrodes which were not stimulated, the behavior of the operator had to be estimated based on available data. Additionally, operators will probably always incorporate their experience when stimulating, hence they will not stimulate suggested electrodes for different reasons, or include others that were not suggested. Prognoses of such ad-hoc decisions is difficult.

Finally, a possible alternative to the current approach would be the utilization of electrode pairs instead of electrodes as guide for ECS. In this case, however, some problems may arise during the transition from functionally significant electrodes to stimulation pairs: (1) the exact locations of the electrodes on the cortex and their distances would need to be known to prepare a meaningful pairs, (2) the transition should be able to determine how often an electrode needs to be stimulated, and (3) the transition should be able to appropriately determine a second electrode for stimulation based on a significant electrode when this electrode is not adjacent to other significant electrodes.

Further studies with more patients are necessary to yield a more conclusive result about the efficacy of the system in terms of reducing the number of required ECS stimulations. One approach could be an analysis of the average numbers of stimulations per patient in ECS-only procedures versus procedures guided by our system, ideally performed by the same investigators. Another approach would be to perform ECS stimulation based on the RTFM suggestions in the beginning. If the result is not satisfying for the operator, more electrodes can be stimulated as required, and the outcome of those additional stimulations is investigated regarding its benefit.

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Preprint submitted to 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Received February 3, 2017.