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Original Article

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Real-Time Functional Mapping with Electrocorticography in Pediatric Epilepsy: Comparison with fMRI and ESM Findings

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Abstract

SIGFRIED (SIGnal modeling For Real-time Identification and Event Detection) software provides real-time functional mapping (RTFM) of eloquent cortex for epilepsy patients preparing to undergo resective surgery. This study presents the first application of paradigms used in functional magnetic resonance (fMRI) and electrical cortical stimulation mapping (ESM) studies for shared functional cortical mapping in the context of RTFM. Results from the 3 modalities are compared. A left-handed 13-year-old male with intractable epilepsy participated in functional mapping for localization of eloquent language cortex with fMRI, ESM, and RTFM. For RTFM, data were acquired over the frontal and temporal cortex. Several paradigms were sequentially presented: passive (listening to stories) and active (picture naming and verb generation). For verb generation and story processing, fMRI showed atypical right lateralizing language activation within temporal lobe regions of interest and bilateral frontal activation with slight right lateralization. Left hemisphere ESM demonstrated no eloquent language areas. RTFM procedures using story processing and picture naming elicited activity in the right lateral and basal temporal regions. Verb generation elicited strong right lateral temporal lobe activation, as well as left frontal lobe activation. RTFM results confirmed atypical language lateralization evident from fMRI and ESM. We demonstrated the feasibility and usefulness of a new RTFM stimulation paradigm during presurgical evaluation. Block design paradigms used in fMRI may be optimal for this purpose. Further development is needed to create age-appropriate RTFM test batteries.

Keywords
epilepsy surgery, pediatrics, functional mapping, functional magnetic resonance imaging (fMRI), brain–computer interface (BCI), SIGFRIED, electrocorticography (ECoG), cortical stimulation

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Introduction

Functional cortical mapping is an essential part of epilepsy surgery programs. The gold standard for functional mapping of language and motor function remains ESM to inhibit selected functional processes.[1] Although the method is routinely used during evaluation prior to epilepsy surgery, it has several drawbacks, including the invasive nature of surgery, the risk of inducing seizures, long testing time, unpleasant sensations induced in patients (especially relevant for the pediatric population), and it is inhibiting normal physiological function, rather than measuring it. Many attempts have been made to perform functional mapping with noninvasive methods, such as fMRI.[2] Although fMRI has proven to be useful, especially in language mapping, and can provide real-time results,[3] it is relatively expensive, time intensive, requires substantial technical expertise, and cannot be performed directly at a patient's bedside.

Recently, technologies have been developed that bridge neurophysiology and computational sciences. These technologies include brain–computer interfaces (BCIs), which analyze

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Full-color figures are available online at http://eeg.sagepub.com changes in spontaneous cortical activation during execution of particular overt or covert tasks. BCI technologies have enabled RTFM of cortical function with minimal additional risk to patients. It does not require the inhibition of physiological processes, as with ESM, but measures normal physiological activity in response to various stimuli, such as sounds, pictures, or words. This novel method allows assessment of the larger neural network involved in the processing of relevant information instead of testing the inhibition of only a limited portion of the circuitry supporting the function, as in the case of ESM.

Whereas both RTFM and ESM procedures are invasive (i.e., they both use grids placed directly on the patients' brain), RTFM relies on interpretation of passively recorded brain signals rather than on stimulation that produce temporary lesions to actively disrupt brain function. RTFM provides an interpretation of physiological brain activation elicited by sound, spoken words or other natural stimuli.

The SIGFRIED software, developed for the general-purpose BCI2000 system,[4] provides RTFM prior to resective brain surgery. SIGFRIED provides real-time bedside visualization of cortical activation during various passive and active tasks that the patient performs. Such mapping for localization of motor function in adults has been shown to be in substantial concordance with those produced using ESM.[5] It has also proven to be useful in intraoperative monitoring.[6]

Whether this novel methodology can be applied to pediatric epilepsy surgical patients, in particular for mapping their language function, was unknown. Moreover, the concordance between functional localization findings with RTFM, fMRI, and ESM has not been previously assessed. In our present study, we provide the first (*a*) assessment of the feasibility and methodological advantages of RTFM-based language mapping using BCI2000/SIGFRIED software[7] in a pediatric epilepsy surgical patient, (*b*) application of paradigms currently used in fMRI and ESM studies for functional cortical mapping in the RTFM context, and (*c*) comparison of the results of functional mapping from 3 different modalities—RTFM, fMRI, and ESM.

Materials and Methods

Subject Description

The Institutional Review Board of the Cincinnati Children's Hospital Medical Center (CCHMC), Cincinnati, Ohio approved the study protocol. The subject was a left-handed 13-year-old male with intractable epilepsy. His typical seizure consisted of right arm stiffening, hand fumbling, and staring. The patient underwent the standard CCHMC preoperative assessment in order to determine the epileptogenic area and eloquent cortex. The evaluation included a neuropsychological exam, seizure characterization by clinical semiology, long-term video-electroencephalography (vEEG), MRI with epilepsy surgery protocol, ictal/interictal SPECT (single-photon emission computed tomography) with subsequent SISCOM (subtraction ictal SPECT co-registered with MRI), FDG-PET (positron emission tomography), MEG (magnetoencephalography), and fMRI.[8]

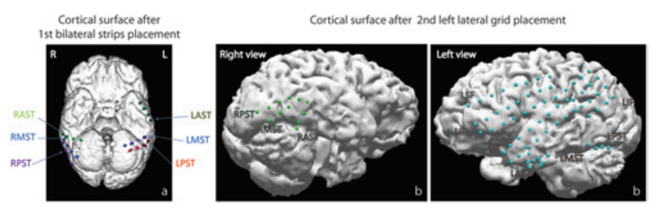

Figure 1. Schematic representation of subdural strip and grid placement for the patient after (A) first surgery with 24 bilateral contact strip placement and (B) second surgery with additional 56 contact grid placements on the left hemisphere (the total number of placed electrodes on both hemispheres is equal to 80). Strips and grids contacts are presented as colored dots on the 3-dimensional model of the brain surface.

Neuropsychological Evaluation

A neuropsychologist performed the neuropsychological evaluation. On the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), the patient scored in the extremely low to average range on the following scales: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Processing Speed Index (PSI), Working Memory Index (WMI), and Full Scale IQ (FSIQ).

Invasive EEG monitoring

Invasive EEG monitoring was recommended, because the noninvasive evaluations revealed incongruent predictions of the suspected epileptogenic zones, and also implicated eloquent functional areas. For invasive monitoring, the patient underwent a 3-step surgical procedure. The goal of the first step was to better lateralize seizure activity. Six 4-contact subdural electrocorticographic (ECoG) strips were placed bilaterally on the anterior subtemporal, medial subtemporal, and posterior subtemporal cortical surfaces (24 electrodes; Figure 1A). After this subdural strip placement, the RTFM procedure was performed. Subsequent to determining that all seizures originated from the left temporal lobe, the second step of the surgery was placement of additional subdural grids (totaling 80 electrodes) that covered the left temporal lobe (Figure 1B, left view). The ESM procedure was performed after additional subdural grid placement. ECoG recordings revealed that the patient had the primary ictal onset in the left temporal lobe (left anterior/subtemporal) with the evolution to right temporal lobe.

Magnetic Resonance Imaging, Computed Tomography, and Electrocorticography Co-registration

A 3-dimensional (3D) volumetric MRI scan performed at 3T (T1-weighted FFE 3D, isotropic 1 mm voxels) and

Table 1. Tasks Presented During RTFM.[a]

Tasks		Mapping Methodology		
Task Name	Task Description	RTFM	ESM	fMRI
Story processing	Involved the auditory presentation of 5 simple stories, each composed of 10 sentences with specifically formulated and complex syntactic constructions that engage multiple brain regions. The control tasks were identical periods of temporally reversed speech (for fMRI) and silent intervals (for RTFM). For this subject, 2 verb generation (finger tap) tasks, and 1 story processing task (reversed speech) were performed[11]	+ (first grid placement)	−	+
Picture naming	Pictures with simple objects (black on a white background) were presented to a subject, and he was asked to name them covertly and overtly[12]	+ (first grid placement)	+	−
Verb generation	Involved the auditory presentation of a series of concrete nouns every 5 seconds. The patient was instructed to covertly (silently) generate as many verbs associated with the noun as possible. The control task was bilateral sequential finger thumb opposition (finger tapping) cued by a target tone played every 5 seconds[13] (for fMRI) and silent intervals (for RTFM)	+ (second grid placement)	−	+

Abbreviations: RTFM, real-time functional mapping; ESM, electrical cortical stimulation mapping; fMRI, functional magnetic resonance imaging.
[a] "+" indicates that the task was performed in the indicated modality and "−" indicates that it was not.

a high-resolution CT scan (512 × 512 matrix, 1-mm slice thickness) were carried out to precisely visualize the location of subdural electrodes on the brain surface. The MRI and CT were co-registered, and 3D segmentation of the brain surface and grid positions was performed using the v.10 AnalyzeDirect (Overland Park, KS).

Functional Mapping

Three types of functional mapping were used to determine localization of eloquent motor and language cortex: fMRI, ESM, and RTFM.

Functional Magnetic Resonance Imaging. fMRI was performed using standardized paradigms for clinical evaluation at CCHMC.[9] The fMRI examination was performed on a Philips 3T Achieva scanner using standard block paradigms for language assessment (Table 1). The paradigms were reviewed with the subject prior to the exam performance. Image processing was performed using Brain Voyager QX (version 2.2.1.1650, Brain Innovations, Maastricht, Netherlands). Preprocessing included 3D motion correction, slice scan time correction, and spatial smoothing using a Gaussian filter (full-width at half maximum = 4 mm). A general linear model logistic regression approach was used for statistical analysis. Co-registered interpolated activation maps were produced and overlaid onto isotropic 1-mm T1-weighted anatomic images using a mutual information algorithm, fine-tuned manually. Clinical statistical maps were made by real-time alterations of significance levels. Both verb generation runs were combined for final statistical analysis. Regions of interests (ROIs) for quantitative analysis were based on prior normative studies in both the frontal and temporal parietal regions.[10] Standard lateralization indices (LI) of activated voxels were calculated between each hemisphere in both the frontal and temporal–parietal regions for verb generation, and the temporal–parietal region of interest for story processing. LI of ≤ -0.2 were deemed to represent right hemispheric lateralization and LI ≥ 0.2 left hemispheric lateralization. Median statistical thresholds for LI calculation were $P < .0007$ (qFDR $< .05$) for story processing, and $P < .00001$ (qFDR $< .05$) for the combined verb generation paradigms.

Electrical Cortical Stimulation Mapping. ESM was performed for identification of language and motor cortex. Stimulations consisted of 5-second trains of 200-ms square-wave pulses of alternating polarity at 50 Hz applied to the adjacent electrode pairs, using an Ojemann Cortical Stimulator (Integra Life-Sciences Corporation, Plainsboro, NJ). Stimulation current intensities were progressively increased beginning at 2 mA to a maximum of 10 mA with 2-mA increments at each cortical site unless after-discharge activity was detected on ECoG. ESM of language functions consisted of picture naming (Table 1).

Real-Time Functional Mapping. Electrocorticography signals recorded from the grids were separated into 2 streams—for clinical recording and for RTFM research in order to ensure recording of the ECoG for seizures remained uninterrupted during our study procedure. For clinical purposes, ECoG signal acquisition was performed together with simultaneous video-recording with the 128-channel Stellate EEG system (Stellate, Quebec, Canada) at a sampling rate of 2000 Hz. For RTFM purposes, the data were acquired using g.USBamp devices (24 bit biosignal amplification unit, g.tec Medical Engineering GmbH, Graz, Austria) at a sampling frequency of 1200 Hz. The ground and reference scalp electrodes were applied to the mastoid, contralateral to the grid placement. BCI2000 with the SIGFIED module were used for signal processing and display visualization. The RTFM procedure was repeated twice—after first and second grid placements (Figure 1).

The SIGFRIED method is described in detail in Schalk et al[7] and Brunner et al.[5] Briefly, the SIGFRIED procedure first estimates the statistical properties of the brain signals recorded during the resting condition. Using the resulting statistical model of the resting condition, it then estimates the likelihood that a new data point is produced by the resting signal distribution. The output of SIGFRIED is the negative log of that probability (so that resulting values are scaled to facilitate visualization). Thus, this output can be expected to be small for samples that are similar to those in the resting signal distribution, and large for samples that are different than those in the resting state distribution.

The following actions were performed during the real-time SIGFRIED procedure: First, the signal from each grid contact was re-referenced, using a common average reference filters. Then, for each grid contact and 500-ms period, the time series ECoG signal was converted into the frequency domain, using an autoregressive model with a model order of 120. 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 100 ms. Finally, for each grid contact and task, the distribution of the negative log-transformed likelihood values was further rereferenced 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.

The results from the signal analyses described above were visualized in real-time using a topographic interface. The interface contained, for each task (ie, story processing), a display of the r^2 values at each location. Each display contained one 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.

The subject sat in front of a screen and was instructed to relax and remain as still as possible. Baseline cortical activity was first recorded for 6 minutes. After that, several paradigms were consequently presented to the subject (Table 1). These included simple tasks that were presented passively, such as story processing (performed after first grid placement), and complex tasks that required the subject's active participation and response, such as picture naming (performed after first grid placement) and verb generation (performed after second grid placement procedure).

Results

Functional Magnetic Resonance Imaging

fMRI revealed atypical language lateralization for both story processing and verb generation paradigms. For verb generation, at median thresholds, there was bilateral, symmetric inferior frontal activation, and more pronounced right lateralization of activation in the temporal parietal regions. LI in the inferior frontal ROI was −0.03, and within the temporal–parietal ROI, −0.94. For story processing, there was bilateral activation in the frontal lobes and more localized right lateralizing activation in the right temporal lobe along the superior temporal sulcus. Temporal–parietal ROI analysis at median statistical threshold resulted in an LI of −0.86. Overall, fMRI results were concordant for right hemispheric lateralization for temporal–parietal language ROI with both paradigms, and indeterminate (but slightly right lateralizing) for frontal lobe language ROI with verb generation.

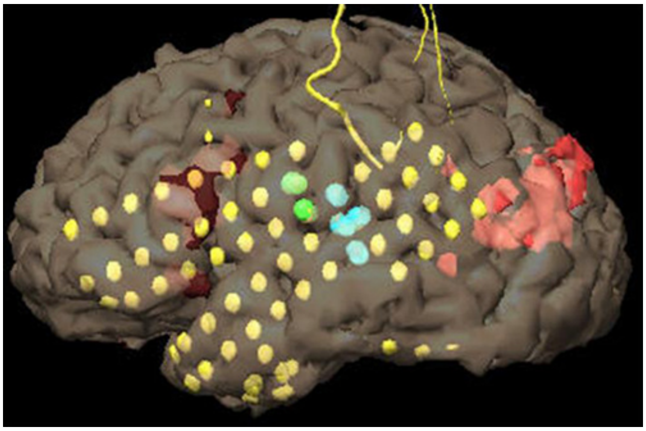

Figure 2. Results of left hemispheric electrical cortical stimulation mapping after second grid placement. Green: Tongue motor. Blue: Sensation of tongue thickness (tongue sensory), no aphasia. Testing of all other grid pairs, including all of the remaining LIF and LLT grid pairs, did not produce significant speech deficits. Yellow dots represent subdural electrodes.

Electrical Cortical Stimulation Mapping

ESM in the left hemisphere demonstrated no eloquent language areas. We observed no significant arrest or interruption of speech responses with ESM during the picture-naming task on either left temporal or frontal expected language areas (Figure 2).

Real-Time Functional Mapping

The RTFM procedure was well tolerated by the patient. Most stimuli paradigms elicited some degree of cortical activation. With the first grid coverage, story processing as well as picture naming elicited activity in the right lateral and basal temporal regions (Figure 3). After the second grid coverage, verb generation task demonstrated atypical language activation, evident in strong right temporal lobe activation together with left frontal lobe activation (Figure 4). RTFM results, indicating atypical right hemisphere dominance for language, correlated well with

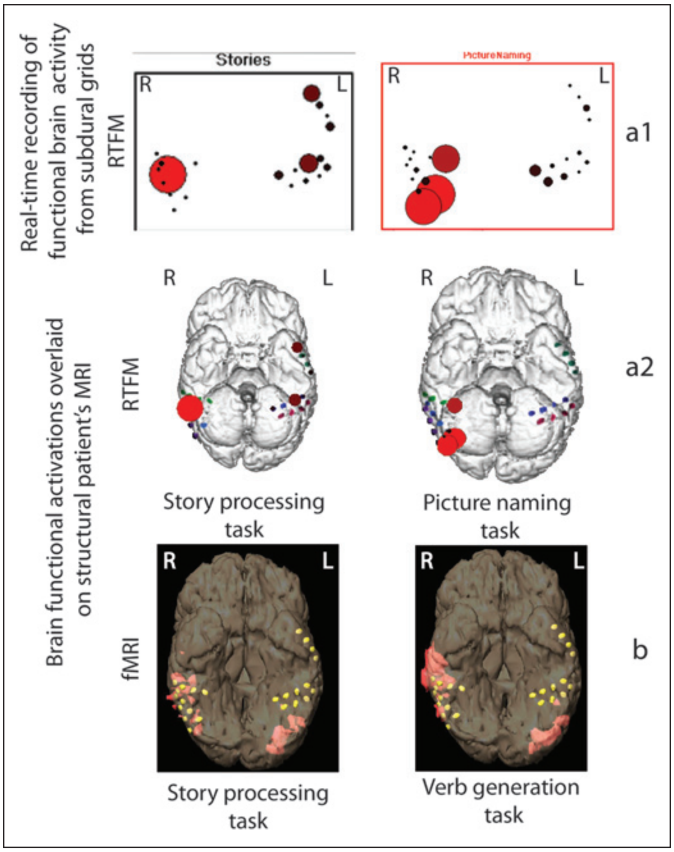

Figure 3. Cortical language activation in epilepsy patient: (A) Results of RTFM recording performed after first grid placement procedure. Cortical RTFM activation maps indicate right-sided language laterlization elicited during picture naming and story processing task. The RTFM responses are maximal in the right lateral and basal temporal regions (locations with significant levels of activation are presented as large red circles; grid placement locations are indicated as red, green, and blue dots); (A1) indicates the response recorded from the grids in real time; (A2) indicates the same response overlaid off-line on the 3-dimensional model of the patient's brain. (B) fMRI activation maps with verb generation and story processing tasks (locations with significant levels of activation are indicated in orange; grid placement locations are indicated as yellow dots). "L" is indicates left hemisphere and "R" indicates right hemisphere.

right-lateralizing fMRI results (as well as indirect ESM results indicating possible right-hemisphere dominance for language). RTFM results for verb generation, after the second grid placement, also were in line with the RTFM results for story processing and picture naming obtained after the first grid placement.

Discussion

We observed right-hemisphere lateralizing language function as directly evidenced from fMRI and RTFM and indirectly from ESM. Such interhemispheric language function reorganization observed in our studied patient is a common phenomenon in patients with left lateralized epilepsy focus.[14] The transfer of language function occurs both intra- and interhemispherically in chronic epilepsy patients, especially when left hemisphere epilepsy develops at an early age.[15] This leads to impairment in nonverbal functions ("crowding" phenomenon),[16-19] as well as deficits in verbal intellectual abilities[20] and academic skills (both reading and spelling).[21] Identifying these changes is of highest priority for epilepsy surgery, as this identification may guide the surgery and consequently improve the likelihood of favorable language functioning after the surgery. In our study, RTFM confirmed abnormal language lateralization evident directly from fMRI data and indirectly from ESM. This case shows that RTFM may correctly identify atypical language lateralization with language transfer from the left to the right hemisphere in patients with chronic epilepsy, which can be due to the presence of pathologic tissue in the language dominant hemisphere. Our study indicates a potential for the RTFM technique to be applied in intraoperative surgical practice in pediatric patients for fast and reliable language mapping complimentary to intraoperative ESM.

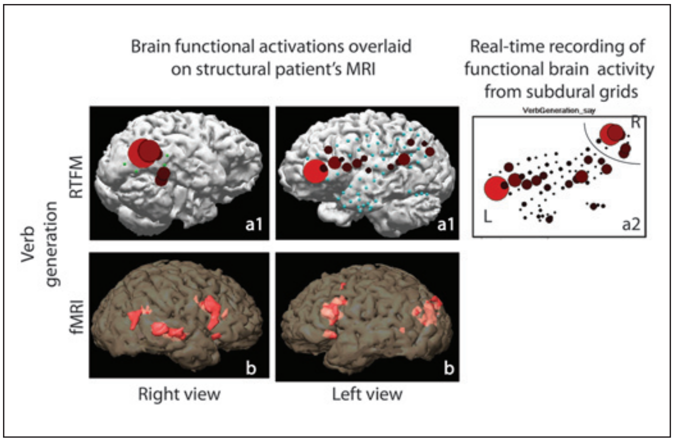

Figure 4. Cortical language activation elicited during verb generation task in epilepsy patient: (A) RTFM activation maps recorded after second grid placement procedure; (A1) represents 3-dimensional model of the brain with off-line over laid activation maps, indicated in picture A2. (B) fMRI activation maps for right and left cerebral hemispheres.

Although the use of RTFM has many advantages, its potential future clinical role, in particular with respect to ESM , is still somewhat unclear. In its emerging clinical use, RTFM is usually employed prior to ESM. Its results are then used to inform and optimize ESM. More specifically, at present the final clinical determinations are still made using ESM,, but RTFM testing is typically useful for choosing cortical sites of lower priority for ESM. This approach may reduce the time of ESM stimulation and, consequently, the possible number of seizures elicited during ESM. This is particularly important for children, who have low tolerance for ESM.

If used alone, one of the most obvious benefits of RTFM would be reduction of time and concomitant increase in cost effectiveness of the presurgical workup. The ESM procedure uses 2 electrodes at a time to create a “lesion” between these 2 locations and observe possible change in function in this particular cortical area. Working with children, we can tell that “mapping” the cortical area located under 128 contacts (pretty standard coverage for children undergoing evaluation for epilepsy surgery in Florida Hospital for Children) may take up to 6 to 8 hours. At the same time, the full evaluation of complete language, motor and sensory function while using RTFM with several repetitions rarely exceeds 2 hours. In general, the results of RTFM are provided within just a few minutes. Importantly, activation under electrodes localized with RTFM is seen as a whole network, whereas ESM provides only single location results after each consecutive stimulation.

RTFM also has more flexibility for presenting language tasks for both receptive and expressive language function than ESM. This is because during RTFM, patients can provide responses within a broader time frame than during ESM, which is restricted in time by electric pulse duration. As a result, additional areas of the brain might be found to be involved in language function than those determined by ESM. Flexibility to present stimuli in time are especially important for mapping language function in children and low-functioning individuals, who need more time to process information and do not have the capacity to respond within the stringent time required by ESM.

As in other imaging modalities (fMRI, MEG), it is of great importance for RTFM testing to use appropriate stimulation batteries. In a previous study by Schalk et al,[7] which concentrated on methodological developments of RTFM technique with SIGFRIED software, vertical cursor movement controlled with motor cortical ECoG activity toward the vertical position of a target was used to identify and assess motor cortex. In another study, Brunner et al[5] employed alternating sequences of repetitive movements of the tongue (protrusion and retraction), and movements of the hand (opening and closing), and resting – similar to those used in ESM protocols. Roland et al[22] used recitation of the alphabet for one of the patients and a part of the Pledge of Allegiance for another one. However, no studies using specific controlled tasks, investigating different aspects of language functions necessary for presurgical evaluation, have been performed. Moreover, none of the paradigms targeted the pediatric population. We used specific test batteries to localize expressive (picture naming, verb generation) and receptive (story processing) language functions. Block design allowed us a close comparison with fMRI findings.

In the future, specific language stimuli corresponding to the cognitive functioning level of the study participant must be developed for RTFM purposes. Future studies may choose to address other important functions, for example, executive, cognitive and emotion-related circuitry, with appropriate, validated, behavioral paradigms, such as recognition of emotions in faces.

Conclusions

Our case study suggests that RTFM appears to be feasible for functional cortical mapping, especially for determining language lateralization in pediatric epilepsy surgery patients. RTFM results confirmed abnormal language lateralization evident from fMRI and ESM. Compared with ESM, RTFM is less likely to induce a seizure, does not interrupt ECoG recording of spontaneous seizures, and provides (*a*) real-time (bedside) visualization of cortical functional activation, (*b*) broad selection of stimulation paradigms, (*c*) opportunity to study patients without requiring active participation (e.g., story processing task), and (4) functional testing soon after grid placement while antiepileptic drugs lowered.

We demonstrated possibilities for new stimulation paradigm implementation of RTFM in presurgical evaluation. A number of different stimuli can be used, and block design paradigms may be optimal. Further development is needed to create age-appropriate paradigm batteries for RTFM.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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