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Case Report

Electrocorticographic mapping of expressive language function without requiring the patient to speak: A report of three cases

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ABSTRACT

Objective: Patients requiring resective brain surgery often undergo functional brain mapping during perioperative planning to localize expressive language areas. Currently, all established protocols to perform such mapping require substantial time and patient participation during verb generation or similar tasks. These issues can make language mapping impractical in certain clinical circumstances (e.g., during awake craniotomies) or with certain populations (e.g., pediatric patients). Thus, it is important to develop new techniques that reduce mapping time and the requirement for active patient participation. Several neuroscientific studies reported that the mere auditory presentation of speech stimuli can engage not only receptive but also expressive language areas. Here, we tested the hypothesis that submission of electrocorticographic (ECoG) recordings during a short speech listening task to an appropriate analysis procedure can identify eloquent expressive language cortex without requiring the patient to speak.

Methods: Three patients undergoing temporary placement of subdural electrode grids passively listened to stories while we recorded their ECoG activity. We identified those sites whose activity in the broadband gamma range (70–170 Hz) changed immediately after presentation of the speech stimuli with respect to a prestimulus baseline.

Results: Our analyses revealed increased broadband gamma activity at distinct locations in the inferior frontal cortex, superior temporal gyrus, and/or perisylvian areas in all three patients and premotor and/or supplementary motor areas in two patients. The sites in the inferior frontal cortex that we identified with our procedure were either on or immediately adjacent to locations identified using electrical cortical stimulation (ECS) mapping.

Conclusions: The results of this study provide encouraging preliminary evidence that it may be possible that a brief and practical protocol can identify expressive language areas without requiring the patient to speak. This protocol could provide the clinician with a map of expressive language cortex within a few minutes. This may be useful as an adjunct to ECS interrogation or as an alternative to mapping using functional magnetic resonance imaging (fMRI). In conclusion, with further development and validation in more subjects, the approach presented here could help in identifying expressive language areas in situations where patients cannot speak in response to task instructions.

1. Introduction

Language is crucial for meaningful interaction and communication. Key language abilities, such as perception and production, are governed by multiple regions in the brain. These abilities can quickly become jeopardized in people with brain tumors, epilepsy, or other structural abnormalities. Many of these patients require resection of pathological tissue near eloquent language areas to prolong or improve quality of life. Inevitably, such resection carries inherent risks to language function. Thus, functional language mapping for precise localization of eloquent language areas is necessary for achieving optimal surgical outcomes in such patients.

Functional language mapping for perioperative planning in individual patients is of utmost importance given the high variability in structural anatomy and function across individuals [1]. Most typically, language mapping is achieved using electrical cortical stimulation (ECS) mapping. While ECS is widely considered the gold standard [1,2], it does

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have noteworthy limitations. First, a thorough ECS interrogation is very time-consuming. Second, ECS increases the risk of after-discharges or seizures that result from "active" stimulation of the cortex using electrical impulses. Finally, ECS can be difficult to accomplish in the subset of pediatric patients and patients with psychiatric and cognitive comorbidities. These issues have prompted recent and increasingly encouraging investigations suggesting that "passive" methodologies, such as electrocorticography (ECoG) or functional magnetic resonance imaging (fMRI), may prove useful for functional mapping and may have distinct advantages in efficiency, morbidity, or the range of patients that can benefit from it [3–11].

Unfortunately, traditional mapping of expressive language function with any of these existing techniques carries the additional requirement that patients actually speak, i.e., fully participate in specific tasks such as verb generation, object naming, or counting. This requirement currently precludes the use of these techniques in many patients, such as those with aphasia or cognitive deficits or very young patients.

Together, these limitations and requirements preclude or greatly impede functional mapping of expressive language areas in certain clinical circumstances (such as during awake craniotomies) or with certain populations (such as pediatric patients). Hence, it is desirable to have access to a technique that does not electrically stimulate the brain and that eliminates or reduces the requirement for patient participation. Such a technique may eventually reduce ECS mapping time by guiding the clinician with a preliminary map of eloquent expressive language cortex. This would not only diminish the risks of patient morbidity, discomfort, and iatrogenic seizures but would also increase the number of patients who could be eligible for functional mapping of expressive language areas.

Identification of eloquent expressive language cortex without requiring the patient to speak is supported by several findings. Previous fMRI studies reported activations of the left [12,13] and bilateral [14–17] inferior frontal gyri while subjects listened to speech stimuli but did not perform any overt speaking task. In addition, Suarez et al. demonstrated using fMRI that a passive listening task recruited similar cortical areas as a verb generation task in a cohort of 15 pediatric patients [17]. However, fMRI is still expensive and requires substantial expertise that is not available in all centers, and its reliability in the context of functional mapping is still uncertain [18,19]. Thus, to date, fMRI-based mapping has not achieved widespread acceptance.

Electrocorticographic recordings also provide opportunities for functional mapping in the context of mapping of motor [2,3,20–22] or language [3,20] function, in pediatric patients [23], and in the operating room [3,6]. Together, these studies demonstrated that ECoG-based mapping can be achieved in real time (i.e., while signals are being recorded), does not require expertise in signal analysis, and can produce clinically useful results that can readily be compared with ECS results in a few minutes. However, evidence for its utility in identifying expressive language without subject participation was lacking. Indeed, only two previous neuroscientific ECoG studies reported activations in the inferior frontal cortex during a passive listening task [24,25], but they did not determine whether these activations could be identified using a common analysis approach, establish the concordance between locations resulting from ECoG- and ECS-based mapping, or discuss the feasibility of such passive mapping ECoG protocol in the context of presurgical or intraoperative mapping. The present report provides initial evidence on this topic from three subjects.

2. Methods

2.1. Patients

Three subjects (A–C) participated in this study. All three subjects were patients at Albany Medical Center (Albany, New York). Subject A was diagnosed with a low-grade glioma in the left frontal lobe after presenting with new-onset seizures. Subjects B and C suffered from intractable epilepsy. All subjects underwent temporary placement of subdural electrode grids to localize seizure foci and eloquent cortex prior to surgical resection. The subjects' clinical profiles are summarized in Table 1. The electrode grids were approved for human use (Ad-Tech Medical Corp., Racine, WI and PMT Corp., Chanhassen, MN) and covered different areas within frontal, temporal, and parietal lobes of the left hemisphere. Most importantly, all three subjects had coverage of frontal lobe language areas, and two of the three (subjects B and C) also had coverage of temporal lobe language areas. Electrodes consisted of platinum–iridium discs (4 mm in diameter, 2.3–3 mm exposed), were embedded in silicone, and were spaced 6–10 mm apart. The total number of implanted electrodes was 61, 98, and 134 in subjects A–C, respectively. Following subdural grid implantation, each subject had postoperative anterior–posterior and lateral radiographs, as well as computer tomography (CT) scans to verify grid location. Preoperative language lateralization (LL) had been assessed previously with fMRI in subject A and with WADA testing [26] in subjects B and C. Based on these evaluations, language was lateralized to the left hemisphere in all three subjects. All subjects signed informed consent to participate in the study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the US Army Medical Research and Materiel Command.

2.2. Data collection

Once subjects recovered postoperatively, we recorded ECoG signals at the bedside using general-purpose BCI2000 software [27,28], which controlled eight 16-channel g.USBamp biosignal acquisition devices (g.tec, Graz, Austria). To ensure integrity of clinical data collection, a connector split the electrode cables into two separate sets. One set was connected to the clinical monitoring system, and another set was connected to the g.USBamp acquisition devices. The ECoG signals were amplified, digitized at 1200 Hz, and stored by BCI2000. We used electrode contacts distant from epileptogenic foci and areas of interest for reference and ground.

2.3. Anatomical mapping

We created 3D cortical brain models for each subject by submitting preoperative high-resolution magnetic resonance imaging (MRI) scans to Freesurfer software (http://surfer.nmr.mgh.harvard.edu/). We coregistered MRI scans with postoperative CT images using SPM software (http://www.fil.ion.ucl.ac.uk/spm/) and identified the stereotactic coordinates of each grid electrode using custom MATLAB scripts (The MathWorks Inc., Natick, MA). Finally, we visualized the cortical surface of each subject and ECoG grid locations using NeuralAct software [29].

2.4. Task and stimuli

In our study, we asked the subjects to listen to four short stories narrated by a male voice (stimulus duration: 17.15–35.70 s; interstimulus interval (ISI) of 10 s) which were part of the Boston Aphasia Battery [30]. The stimuli were digitized at 44.1 kHz in waveform audio file format and binaurally presented to each subject using in-ear monitoring earphones (12 to 23.5 kHz audio bandwidth, 20 dB isolation from

Table 1
Clinical profiles of the 3 patients. "LL" reflects language lateralization.

Subject	Age	Sex	Handedness	LL	Seizure focus	Grid location	# of elec.
A	34	M	R	L	Left frontal	Left frontal	61
B	28	M	R	L	Left temporal	Left frontal	52
						Left temporal	66
						Left parietal	16
C	25	F	R	L	Left temporal	Left frontal	28
						Left temporal	66
						Left parietal	4

environmental noise). The sound volume was adjusted to a comfortable level for each subject. The subjects did not perform any overt task (such as repeating words and generating verbs in response to the words they heard).

2.5. Feature extraction

We identified ECoG activations by detecting task-related changes in the broadband gamma (70–170 Hz) band. Activity in this band has been shown to be related to the average firing rate of neuronal populations directly underneath an electrode [31–33]. A large number of studies have shown that broadband gamma activity increases reliably in task-related cortical areas [20,34], including locations traditionally thought to be active during speech perception [24,35,36].

To identify those locations that responded to auditory stimulation, we first removed channels that did not contain clear ECoG signals (e.g., ground/reference channels, channels with broken connections, or channels corrupted by environmental artifacts or interictal activity). Of a total of 61, 98, and 134 channels, this left 59, 79, and 132 channels for subjects A–C, respectively, which we submitted to subsequent analyses. In these analyses, we high-pass filtered the signals at 0.1 Hz to remove drifts and re-referenced the signals to a common average reference (CAR) montage. We band-pass filtered the results in the broadband gamma band using a Butterworth filter of order 16. We then obtained the power of these signals by computing the square of the analytical signal of the Hilbert transform, followed by a low-pass filter at 4 Hz and down-sampling to 120 Hz. Finally, we normalized the resulting broadband gamma power estimates by subtracting from them the signal mean calculated from a baseline period (−6 to −0.5 s prior to the onset of the auditory stimulus) and by dividing them by the standard deviation of the signal during the baseline period.

2.6. ECoG-based mapping of expressive language cortex

We determined those locations whose ECoG broadband gamma activity following onset of the auditory stimulus (i.e., the response period) was different from that during the baseline period. Several studies have shown that, in receptive auditory areas, broadband gamma activity reliably tracks the time course of the envelope of the intensity of the auditory stimulus [37,38] or speech stimulus [39]. A few isolated reports documented discrete and brief broadband gamma activations in inferior frontal cortex after the onset of an auditory speech stimulus [24,25] that occurred after the activations in receptive auditory areas [25]. Based on these reports, we defined the response period as 250–750 ms following the onset of the auditory stimulus. Then, for each location, we determined the magnitude of the change in ECoG broadband gamma power that was related to auditory stimulation by calculating the coefficient of determination (Pearson's r^2 value). Finally, we determined the statistical significance of each r^2 value, i.e., the probability that ECoG broadband gamma samples differed in amplitude between the response and baseline periods, using a permutation test. In this test, we cut the ECoG broadband gamma power time courses into blocks of 500 ms (thereby preserving the autocorrelation of the signal), randomly permutated the resulting blocks, and finally calculated the corresponding random r^2 value. We repeated the permutation step 1000 times, thus generating a distribution of 1000 random r^2 values at each location. We considered r^2 values to be significant at the 95th percentile of that distribution ($p = 0.05$, Bonferroni-corrected for the total number of electrodes in each subject). The result of this procedure was a set of locations whose ECoG broadband gamma activity was significantly different between the baseline and the response periods and, hence, responded to the speech stimuli. Among the resulting locations, we identified those that were situated within inferior frontal cortex. This included all electrodes whose Talairach [40] coordinate was within x −28 to −55, y −8 to +34, and z 0 to 28, consistent with previous observations [41].

2.7. ECS-based mapping of expressive language cortex

Standard electrocortical stimulation mapping of expressive speech was performed extraoperatively for clinical purposes. The subjects took part in two simple tasks commonly used for this purpose: a picture-naming task, during which subjects were asked to verbally name sequentially presented pictures of simple objects and a verb generation task, during which subjects had to verbally generate verbs associated with simple nouns presented auditorily. Different electrode pairs were stimulated to establish whether a given pair induced a disruption of expressive language function, e.g., speech arrest or hesitation. Stimulation intensity typically started at 2 mA and was increased in incremental steps of 2 mA until the neurologist observed clinical effects or after-discharges or reached the 10 mA threshold.

3. Results

The main results of our study are presented in Fig. 1. This figure highlights those locations that were identified by our analyses of the ECoG signals corresponding to the presentation of the speech stimuli (filled circles) and locations that produced arrest of expressive language function using ECS mapping (yellow circles).

Locations identified by ECoG mapping included the expected locations (highlighted by gray-filled circles) in superior temporal gyrus and/or perisylvian areas (all subjects) as well as in premotor and/or supplementary motor areas (subjects A and C) [38]. Consistent with previous observations (see Fig. 8 in [38]), our method also identified responsive locations on or close to superior precentral gyrus (Patient C). Most relevant in the context of the present study, our ECoG-based mapping identified locations (highlighted by blue-filled circles) in inferior frontal cortex (pars triangularis and/or pars opercularis) in all three subjects. Fig. 1C also presents exemplary time courses of ECoG broadband gamma activity in Patient C.

Electrical cortical stimulation mapping identified 1–2 locations in which stimulation produced expressive language arrest in each subject (yellow circles). These locations were also located in or around pars triangularis and pars opercularis. The ECS-positive sites overlapped with the sites identified using ECoG or were located no more than one contact away.

4. Discussion

In our study of three patients with chronically implanted subdural electrode grids, we provide initial evidence that it is possible to use passively recorded ECoG in response to presentation of speech stimuli to identify not only locations in the receptive language network that are located primarily in the temporal lobe but also locations within the expressive language network in the inferior frontal cortex.

With further refinement of the protocol and validation in more subjects, the passive mapping approach described here could lead to a mapping method that may have important clinical implications. The ability to map expressive language cortex with greatly reduced needs for patient participation expands the utility of functional language mapping. Specifically, it enables functional mapping of expressive language in patients who are unable to cooperate productively such as pediatric populations or patients suffering from aphasia or psychiatric and cognitive comorbidities. We envision passive language mapping using ECoG to either complement existing ECS or fMRI mapping protocols or provide an alternative when other expressive language mapping techniques are inadequate. The ECoG passive mapping may also have distinct advantages in the time-limited settings of the intraoperative environment. A preliminary map of eloquent expressive language cortex could inform ECS mapping, likely resulting in reduced ECS mapping time and thereby diminishing the risks of patient morbidity, discomfort, and iatrogenic seizures. This would prove extremely useful in an intraoperative decision-making situation. Recent studies already

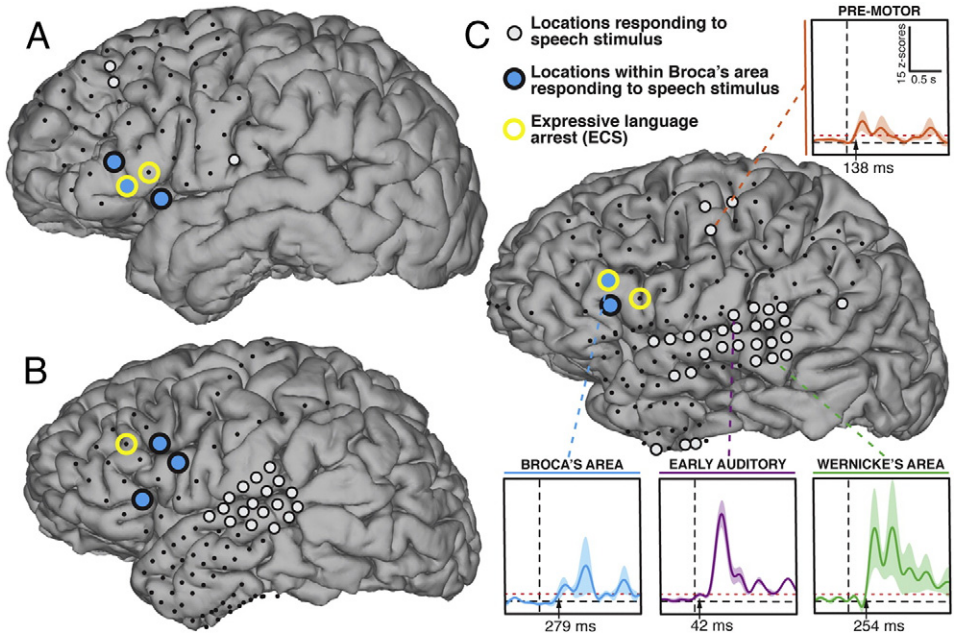

Fig. 1. In this figure, panels A–C reflect results for the patients A–C, respectively. The electrode locations for each patient are overlaid in black, while white, blue, and yellow circles correspond to locations described in the legend above. Panel C also includes four graphs presenting ECoG activity over exemplary sites from −500 ms to 1500 ms after stimulus onset. Shaded areas reflect the standard error of the mean, the vertical dashed lines show stimulus onset, the horizontal dashed lines show baseline activity, and the horizontal dotted red lines show a 3 z-score threshold above which ECoG activity is significantly different from baseline. The exact timing at which ECoG activity passes this threshold is further denoted by an arrow under each time plot.

demonstrated the feasibility of intraoperative real-time mapping of motor [3,6] and language [3,6,42] mapping using acutely placed subdural grids.

4.1. Variable congruency between ECS and ECoG

One important general question that remains to be answered is the reason for the variable congruency between ECS and passive ECoG in the context of language mapping. Using traditional ECoG-based mapping tasks (such as verb generation, picture naming, and passive listening), previously reported concordance rates between ECoG and ECS range from 38%–89% in sensitivity and from 48%–92% in specificity [4,23,43,44]. This variability in concordance reported in the literature can be attributed to several factors. These include the different language tasks used with each modality [44,45]. Other potential explanations for the discrepancies between ECS and ECoG involve the statistical issues that necessarily result from the comparison of the single-electrode ECoG method with the pair-wise ECS method [2,45] and the fundamental difference between a lesion-based model approach versus a task-based physiologic approach [34,43]: while ECoG should identify all locations at which neuronal populations subserve the specific function, ECS will only identify the (potentially small) subset of those locations that completely disrupt function. Thus, ECoG can be expected to define a larger area for preservation and underestimate the margin for safe resection. In this context, it is worth noting that patients have been reported to have postoperative language deficits after resection of an ECoG(+)/ECS(−) node [4,23,43,44,46,47]. In a study of 77 patients, postoperative language deficits could be predicted by the number of ECoG(+) language nodes resected [48]. At present, most resections are based primarily on ECS results even though ECS has never been validated in randomized, clinical trials [2]. This reality implies that, with continued refinement and validation, the ECoG method may play an even larger role in presurgical functional mapping in the future. At the same time, without additional information, we currently do not suggest replacing exhaustive ECS mapping but rather argue that ECoG-based mapping provides useful and complementary information.

4.2. Additional evidence from other studies supports the mapping of expressive language function without requiring the patient to speak

Another critical question raised by the present study is to what extent the encouraging results presented here generalize to a larger number of patients. For two reasons, we are optimistic that the results in a larger number of patients will echo the initial results reported here. First, several groups have reported activation of the inferior frontal gyrus in response to presentation of passive speech stimuli [12–15,17,49]. Mazoyer et al. first demonstrated activation of the left inferior frontal gyrus on positron emission tomography (PET) scans in 16 subjects while listening to lists of words and stories [12]. Several fMRI [13–15,17,49] and ECoG [24,25] studies have replicated these results using similar tasks. Furthermore, it is well known that the blood-oxygen level-dependent (BOLD) signal changes detected using fMRI correlate very well with the broadband gamma increases in ECoG [50–56], which are the basis of ECoG-based functional mapping. Second, recent evidence indicates that ECoG-based mapping can identify locations in expressive language areas when sites in receptive language areas are stimulated using electrical stimulation (corticocortical evoked potentials (CCEPs)) [57–60]. For example, Matsumoto et al. [57] described the technique of delivering a single pulse electrical stimulation in the inferior frontal language area and recording a cortical evoked potential in the temporal–parietal area, establishing structural neuronal connectivity between the two functional regions. In a smaller subset of patients, they were able to elicit CCEPs in the inferior frontal and basal temporal regions with stimulation of the temporo–parietal language area. This bidirectional connectivity is likely mediated at least in part by the arcuate fasciculus, although the anatomical distribution of the arcuate fasciculus may be more complex than historically assumed [61–64]. More generally, the language network connectivity model appears to be much more complex than initially believed, with

an interplay of numerous cortical regions and white matter tracts [62,65–67].

4.3. Study limitations

While our initial results are encouraging, different circumstances could temper the significant positive implications of expressive language mapping using passive stimuli. When applied in intraoperative scenarios, different surgical realities (such as intermittent irrigation on the subdural grid, cable adjustment, variable clinical or cognitive status of the patient) may lead to lower signal-to-noise ratio and a resultant decrease in ability to detect task-related ECoG changes. The duration of mapping may be increased if the grid requires repositioning with reinitiation of tasks. Furthermore, it is possible that passive engagement of expressive language function may not elucidate the whole expressive language network. Finally, the current study is only reporting results for 3 subjects. Further investigation in a larger number of patients is required to assess the potential benefit of our findings to resective neurosurgical planning. Furthermore, while our method successfully identified expressive language sites in a patient diagnosed with a left frontal tumor in close proximity to Broca's area (subject A), it is not possible to predict how our method would generalize to patient populations with different types of distorting pathologies. It would also be valuable to determine if our method can identify eloquent expressive language cortex in patients with aphasia.

5. Conclusions

In this paper, we report initial results of an approach to functional mapping of expressive language function that could greatly reduce the need for subject participation. With further refinement and validation, the approach described here may lead to a simple, easy-to-use protocol that would simultaneously identify receptive and expressive language areas for surgical planning. This protocol would be widely applicable in a significantly greater number of patients. Finally, because our approach does not require the patient to speak, it opens up the possibility for applying it to patients under general anesthesia. Thus, this approach has the potential to completely revolutionize functional language mapping in neurosurgery; the initial results presented here clearly encourage further investigation.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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