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Passive functional mapping of receptive language areas using electrocorticographic signals

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HIGHLIGHTS

- Broadband gamma mapping identified receptive language areas in 22 of 23 subjects.
- Comparison with stimulation mapping resulted in 95% sensitivity and 59% specificity.
- 82% of contacts identified using broadband gamma were within 1.5 cm of an ECS+ site.

ABSTRACT

Objective: To validate the use of passive functional mapping using electrocorticographic (ECoG) broadband gamma signals for identifying receptive language cortex.
Methods: We mapped language function in 23 patients using ECoG and using electrical cortical stimulation (ECS) in a subset of 15 subjects.
Results: The qualitative comparison between cortical sites identified by ECoG and ECS show a high concordance. A quantitative comparison indicates a high level of sensitivity (95%) and a lower level of specificity (59%). Detailed analysis reveals that 82% of all cortical sites identified by ECoG were within one contact of a site identified by ECS.
Conclusions: These results show that passive functional mapping reliably localizes receptive language areas, and that there is a substantial concordance between the ECoG- and ECS-based methods. They also point to a more refined understanding of the differences between ECoG- and ECS-based mappings. This refined understanding helps to clarify the instances in which the two methods disagree and can explain why neurosurgical practice has established the concept of a "safety margin."
Significance: Passive functional mapping using ECoG signals provides a fast, robust, and reliable method for identifying receptive language areas without many of the risks and limitations associated with ECS.

1. Introduction

Resective brain surgery for the treatment of tumors or intractable epilepsy often requires localizing "eloquent" cortical regions involved in production and comprehension of language to minimize post-surgical deficits. Among the techniques to identify these eloquent regions, electrical cortical stimulation (ECS) has become the gold standard, perhaps because of its relatively low cost and procedural simplicity (see Borchers et al., 2012 for review).

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While its utility is undisputed, the use of ECS does have noteworthy limitations that include substantial time requirements (typically several hours (Hamberger, 2007; Ritaccio et al., 2018)), an increased risk for induced pathological brain activity such as after-discharges or seizures (Corley et al., 2017), and common difficulties with pediatric and other populations (Chitoku et al., 2001; Korostenskaja et al., 2014a; Paus et al., 1999). These issues are exacerbated in the intraoperative scenario and lead to increased morbidity (Nossek et al., 2013). Additionally, post-surgical evaluation of potential functional deficits have been conducted in a small number of studies but are not the norm (Haglund et al., 1994; Ojemann and Dodrill, 1985), which greatly impedes full characterization of the efficacy of ECS or other methods (see Hamberger, 2007 for review). A practical, rapid, accurate, and safe mapping method may improve post-surgical outcomes and may supplement or eventually replace ECS. Several studies have shown that passive functional mapping using electrocorticographic (ECoG) signals in the broadband gamma band (70–110 Hz) can safely and rapidly localize eloquent cortex in only a few minutes (Korostenskaja et al., 2014a; Babajani-Feremi et al., 2016; Brunner et al., 2009; Crone et al., 1998; de Pesters et al., 2016; Kapeller et al., 2015; Korostenskaja et al., 2014b; Leuthardt et al., 2007; Miller et al., 2007, 2009, 2011; Roland et al., 2010; Schalk et al., 2008; Taplin et al., 2016; Wang et al., 2016; Towle et al., 2008). Within the domain of language function, most studies have assessed the utility of ECoG mapping to localize expressive language cortex (Babajani-Feremi et al., 2016; de Pesters et al., 2016; Miller et al., 2011; Taplin et al., 2016; Wang et al., 2016); corresponding studies for receptive language mapping have been scarce (but see Korostenskaja et al., 2014a; Towle et al., 2008).

Here we describe the first large-scale study ($n = 23$) that uses passively recorded ECoG signals to map receptive language function and that compares the results to those derived from ECS mapping in the 15 subjects for whom ECS results were available. Our results show that ECoG mapping reliably identified receptive language areas in less than 4 min, and that these areas showed a high degree of concordance with those identified using ECS. Furthermore, they point to a more refined understanding of the differences between ECS- and ECoG-based mapping, which can explain why neurosurgical practice has established the concept of a 10- to 20-mm “safety margin” (Haglund et al., 1994; Ojemann and Dodrill, 1985).

2. Methods

2.1. Subjects

A total of 23 patients with intractable epilepsy underwent temporary placement of subdural electrode grids at Albany Medical College (Albany, NY) to localize seizure foci and, when clinically indicated, to also localize eloquent language cortex using ECS mapping prior to surgical resection. All patients were native English speakers and completed pre-surgical neuropsychological evaluations. All patients had standard clinical followup, and none had residual receptive, expressive, or anomic deficits. At the same time, comprehensive post-operative neuropsychological testing was not performed in any subject. The clinical profile of the patients is summarized in Table 1. All patients gave informed consent for this study, which was approved by the Institutional Review Board of Albany Medical College and the Human Research Protections Office of the U.S. Army Medical Research and Materiel Command. Electrode grids were placed solely on the basis of clinical necessity (i.e., without any consideration of this study). Grids consisted of platinum-iridium electrodes (4 mm in diameter, 3 mm exposed, 6–10 mm inter-electrode spacing) embedded in a Silastic sheet. Subject V was implanted with a high-density electrode grid that had 250 contacts (2 mm in diameter, 1 mm exposed, 3 mm inter-electrode spacing). Preoperative MRI depicted the cortical anatomy; postoperative CT imaging localized the electrodes. We created three-dimensional cortical models for each patient using preoperative MRI images and the freely available software package FreeSurfer (https://surfer.nmr.mgh.harvard.edu). To localize electrode locations on each cortical model, we co-registered these MRI images with post-operative CT using Curry software (Compumedics, Charlotte, NC) or the MATLAB toolbox SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Finally, we generated visualizations of electrodes on each subject’s cortical model using our NeuralAct software package (Kubanek and Schalk, 2015).

Table 1

Clinical profile of the 23 subjects in this study. All subjects had normal cognitive capacity and were literate and functionally independent. Language lateralization was based on WADA tests and/or functional magnetic resonance imaging (fMRI). Number of electrodes analyzed represents the total number of electrodes implanted after removing those affected by artifacts. All subjects who had an ECS mapping performed ($n = 15$) were considered for quantitative comparisons between ECS and passive mapping outcomes.

Subj.	Age	Sex	Hand. Dom.	Verb. IQ	Grid Hem.	Lang. Dom.	Electr. Impl.	Electr. Anal.	# ECoG+	# ECS+	# Stim.
A	24	M	R	83	R	L	99	98	8	3	66
B	26	F	R	106	L	L	109	103	1	N/A	N/A
C	56	M	R	82	L	L	97	94	1	N/A	N/A
D	45	M	R	93	L	L	58	56	15	N/A	N/A
E	49	F	L	91	L	L	72	68	7	3	43
F	29	F	R	111	L	B	120	118	10	N/A	N/A
G	25	F	R	84	L	B	128	118	5	2	107
H	18	F	L	117	L	L	94	94	10	2	52
I	15	F	R	91	R	N/A	69	61	0	0	59
J	22	M	N/A	78	R	N/A	81	77	4	0	31
K	28	M	R	114	L	L	134	116	16	N/A	N/A
L	25	F	R	91	L	B	98	78	17	2	47
M	54	M	L	116	R	L	76	65	10	6	28
N	44	M	L	91	L	R	81	79	8	0	40
O	25	F	R	103	R	N/A	79	78	4	1	49
P	21	F	R	N/A	R	N/A	136	135	4	N/A	N/A
Q	20	F	R	81	L	L	90	89	14	5	28
R	36	M	R	76	R	B	92	91	1	0	10
S	40	F	R	91	R	N/A	117	113	8	N/A	N/A
T	33	M	R	N/A	L	N/A	114	110	9	N/A	N/A
U	57	F	R	N/A	L	N/A	98	94	9	4	54
V	33	F	R	92	R	N/A	250	237	70	0	9
W	17	F	N/A	N/A	L	N/A	74	73	13	8	74

2.2. ECS mapping

ECS mapping was clinically indicated for 15 of 23 patients and took 1.5–7.5 h to perform. During this procedure, the patients were asked to perform typical sentence completion and language comprehension tasks while electrical stimuli were applied (trains of up to 10 s, 300 μs biphasic pulses, 50 Hz frequency). See Hamberger (2007) and Ritaccio et al. (2018) for a review of ECS mapping. Stimulation current levels usually began at 2 mA for each stimulation pair to test for after-discharges. If after-discharges were detected, current was ramped up in 2-mA steps until receptive language inhibition was observed or the current level reached 10 mA. If no after-discharges were detected at 2 mA, current amplitude was set immediately to 10 mA. The reliability of the language inhibition was verified through multiple stimulation trials, including sham trials where no stimulation current was delivered. ECS resulted in reliable inhibition of receptive language function in 10 of the 15 stimulated subjects.

2.3. Data collection

We acquired ECoG signals from 58 to 250 electrode contacts at the patients' bedsides using either one g.HIamp (g.tec, Graz, Austria) or eight synchronized g.USBamp (g.tec, Graz, Austria) biosignal amplifier(s). Data collection and stimulus presentation were accomplished using the BCI2000 software platform, a general-purpose system for real-time biosignal acquisition, processing, and feedback (Schalk et al., 2004, 2000). BCI2000 interfaced with the biosignal amplifiers to acquire ECoG signals, digitize them at 1200 Hz, and store them locally on a computer at the bedside. Electrode contacts distant from seizure foci and from the anticipated anatomical location of eloquent cortex were used as ground and reference electrodes, respectively. Electrodes affected by significant signal artifacts or those that did not contain clear ECoG signals (i.e., ground/reference, electrodes with broken leads, environmental or physiological artifacts) were removed, which left 56–237 electrodes for subsequent analyses.

2.4. ECoG mapping protocol

Each subject listened to four short stories from the Complex Ideational Material (CIM) subtest of the Boston Diagnostic Aphasia Examination (BDAE) as a surrogate for day-to-day listening activities (Korostenskaja et al., 2014b; Goodglass et al., 2001). These stories were presented through loudspeakers at a comfortable volume while the words "Listen carefully" were presented on a computer screen. The length of the stories varied from 17 to 36 s, and each story was presented twice in a block-randomized fashion (3:26 min total duration). Each story was followed by a 15-s rest period while the word "Relax" was presented on the screen. It is important to note that this type of auditory stimulation engages the whole receptive language system, i.e., not only cortex that supports the linguistic concepts of "language" or "speech," but also lower-level auditory areas. This concept is similar to that employed with tasks used during conventional ECS mapping (such as word comprehension or repetition), which also depend on intact function of the whole receptive language system. While surgical resection planning only considered ECS mapping results, resection spared all sites identified with both ECS and ECoG mapping.

2.5. ECoG signal processing

We then identified the cortical locations whose ECoG broadband gamma activity changed while the subjects listened to the stories. (Broadband gamma activity has been shown to be a reliable indicator of neuronal activity directly underneath an electrode (Lachaux et al., 2007)). To do this, we first eliminated common noise by re-referencing the ECoG signals to a common average reference (CAR). We then extracted broadband gamma activity by bandpass-filtering (70–110 Hz, 4th-order Butterworth filter), followed by a Hilbert transform. To determine which ECoG locations increased their broadband gamma activity during the listening task, we applied a bootstrap test (using 1000 randomly assigned listening and relax periods) to determine, for each location, the statistical significance of the difference in mean broadband gamma activity between listening and relax periods. We defined those locations as statistically significant where p was smaller than 0.05 after Bonferroni correction for the number of electrodes in that subject.

3. Results

3.1. Qualitative results

The ECoG-based mapping results from all 23 subjects are shown in Fig. 1. Each cortical model represents one subject and indicates the electrode locations as black and red circles. Electrodes whose broadband gamma activity was significantly increased during the listening task are indicated in red (ECoG+). The diameter of each red electrode is related to the magnitude of statistical significance, i.e., the negative logarithm of the p value. A summary of broadband gamma amplitudes during the baseline (median: 2.4 μV), as well as the range of task-related amplitude increases considered significant (12–83%) is given in Supplementary Table 1. The comparison between ECS- and ECoG-based results is shown in Fig. 2 for the subset of 10 of the 23 subjects for whom ECS resulted in inhibition of language function. Blue circles indicate the electrodes for which this inhibition was reliably observed (ECS+).

3.2. Quantitative results

The ECoG-based mapping results in Fig. 2 suggest a high concordance with ECS-based mapping results. To quantify the degree of concordance, we determined the sensitivity and specificity of the ECoG-based mapping results with respect to the ECS maps using a next-neighbor approach. We calculated sensitivity and specificity as in Brunner et al. (2009) according to the following equations in which T_P is the true positive rate, F_P is the false positive rate, T_N is the true negative rate, and F_N is the false negative rate: Sensitivity = $T_P/(T_P + F_N)$, Specificity = $T_N/(T_N + F_P)$.

The results show an average sensitivity of the ECoG-based mapping method of 95% (±5.0%) and an average specificity of 59% (±7.3%) for the 15 subjects on whom ECS mapping was performed. Additionally, a paired t-test shows significantly more active sites identified using ECoG-based (6.7 ± 1.2) compared to ECS-based (2.4 ± 0.6) mapping ($p < 0.001$). Only stimulated sites were considered. Active sites are represented as mean ± SEM. The results of this analysis are summarized in Table 2.

Consistent with the literature, these results indicate a high level of sensitivity and a lower level of specificity. At the same time, we noticed that the ECoG+ results tended to cluster around the ECS+ results, forming what could be termed a "functional penumbra." On the basis of this observation, we believe that the relationship between ECS+ and ECoG+ sites may be better captured by the fraction of ECoG+ sites that were within a certain distance from the ECS+ sites. The results shown in Table 2 and Fig. 3 indicate that

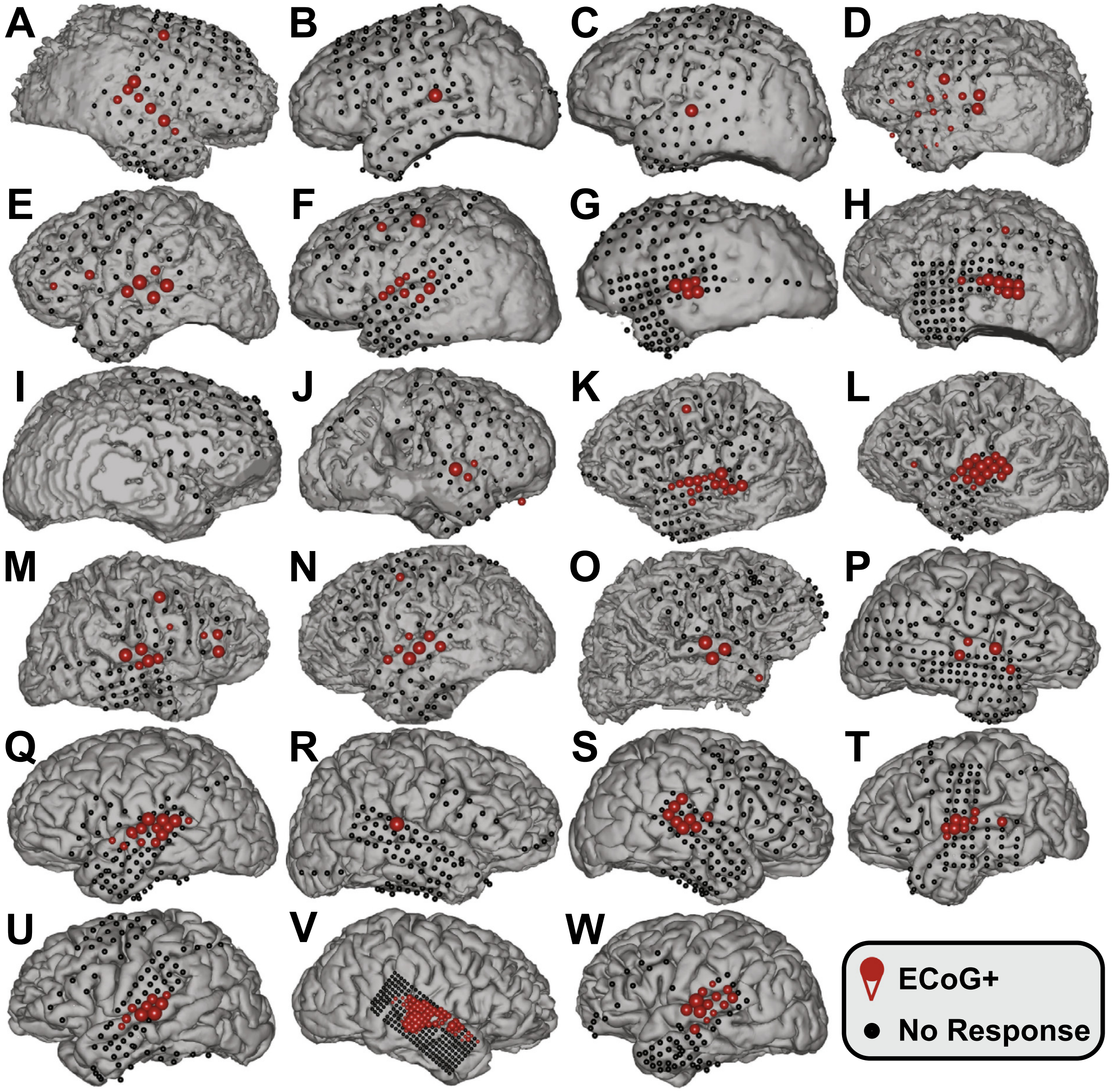

Fig. 1. ECoG-based mapping of receptive language activity. Electrode locations for each of the 23 subjects are shown as black or red circles. Electrodes affected by significant signal artifacts or those that did not contain clear ECoG signals are indicated by small white circles. Electrodes whose broadband gamma activity significantly increased during the listening task are shown as large red circles. The diameter of each red electrode is related to the magnitude of task-related ECoG broadband gamma modulation (see Methods). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

82% (± 7.1%) of the ECoG+ sites were within one contact of the ECS+ sites in the 10 subjects who had an ECS response.[1]

4. Discussion

In the largest study of its kind to date, we here provide an evaluation of passive functional mapping of receptive language in 23 patients with epilepsy. The results show that current ECoG-based mapping methods support practical, effective, and efficient localization of receptive language areas (i.e., any area supporting any aspect of auditory or linguistic function) in 22/23 patients. Additionally, we observed a high degree of concordance in the 10/15 subjects for whom ECS+ results were available. None of the subjects in this study underwent fMRI mapping of language function, although a comparison between passive functional mapping and fMRI has been demonstrated in Korostenskaja et al. (2014b). ECoG-based mapping can be accomplished at the bedside, can be completed in under 4 min, is procedurally simple, and has recently become widely available (Kapeller et al., 2015). Mapping results readily identify eloquent sites in the temporal lobe in all subjects with appropriate coverage when a subtest of the Boston Diagnostic Aphasia Examination is applied to simulate everyday listening activities. The regions outlined by these sites are qualitatively highly concordant to the sites identified using electrical stimulation.

Despite this high qualitative concordance, quantitative concordance (95% sensitivity, 59% specificity) was not perfect. Indeed, in contrast to mapping of motor function, which has consistently resulted in very close agreement between ECS- and ECoG-based mapping (Brunner et al., 2009; Kapeller et al., 2015; Leuthardt et al., 2007), mapping of language function shows a modestly

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[1] The implanted electrodes had 6- or 10-mm spacing. We here define “within one contact” as those electrodes that were less than 1.5 cm away, which includes the next-neighboring electrodes in a standard grid with 10-mm spacing.

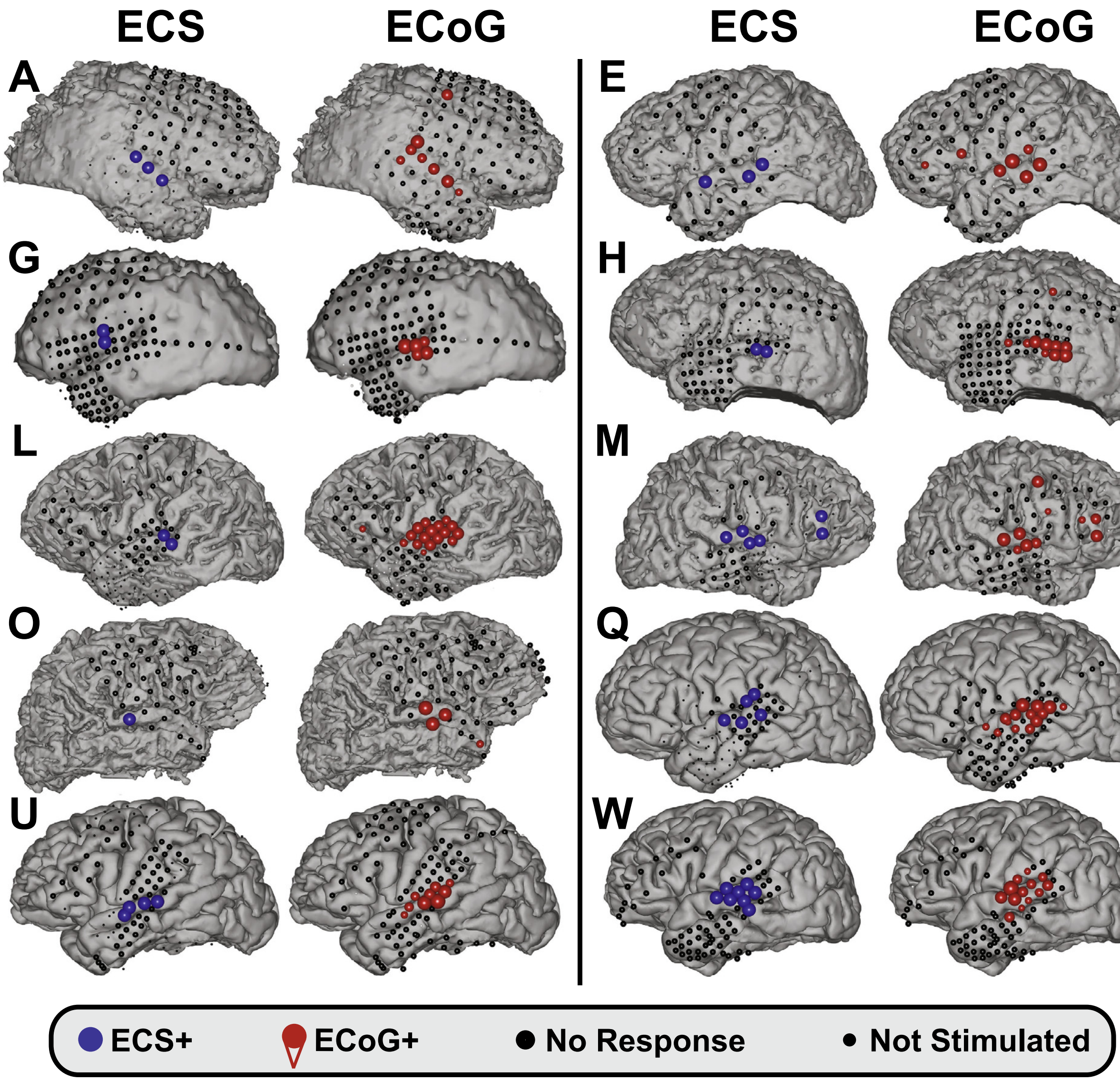

Fig. 2. Comparison between ECS- and ECoG-based mapping methods. Electrode locations for each of the 10 subjects with ECS-induced language inhibition are shown as black, blue, or red circles. Electrodes affected by significant signal artifacts or those that did not contain clear ECoG signals are indicated by small white circles. Electrodes whose broadband gamma activity significantly increased during the listening task are shown as large red circles (ECoG+). The diameter of each red electrode is related to the magnitude of task-related ECoG broadband gamma modulation (see Methods). Blue circles indicate electrodes for which ECS-induced language inhibition was reliably observed (ECS+). Large black circles indicate electrodes without ECS-induced inhibition of language function (i.e., "No Response"), while small black circles indicate electrodes that were not stimulated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

higher degree of discrepancy. For example, Sinai et al. (2005) reported a sensitivity of 38% and specificity of 78% for language mapping. Miller et al. (2011) reported a sensitivity of 89% and specificity of 66% for a noun reading task, and a sensitivity of 74% and specificity of 48% for a verb generation task. Finally, Korostenskaja et al. (2014b) documented a sensitivity of 75% and specificity of 90% when using the next-neighbor approach. Previous discussions of this topic have centered on the different tasks used by the two methods and on the fundamental differences between them. Specifically, ECS is an active and causal method that disrupts cortical networks that are critical for a particular function, whereas ECoG is a passive and correlational method that highlights all cortical populations that are engaged by a particular task (Su and Ojemann, 2013). Furthermore, ECoG-based mapping assigns a function to individual electrodes, whereas ECS usually assigns it to both the anode and cathode electrode. (This circumstance motivates the next-neighbor approach of analysis.) While clearly reasonable, these explanations appear relatively descriptive and do not provide a satisfactory explanation of differences in mapping results across methods. For example, while it is possible that neuronal activation detected with the ECoG method originates from neurons that participate in a task without in any way causally contributing to task-related function, we deem it unlikely that the brain expends precious energy on unnecessary neuronal activation. Moreover, it is clear that ECoG+ sites are not randomly scattered across the cortical surface but rather index cohesive regions on and around those identified using ECS, even though corresponding specificity values can be very low. For example, the ECoG+ sites shown for subject Q in Fig. 2 appear quite similar to the ECS+ sites, but the specificity value for this example is only 9%.[2] As a further complication, current methods of evaluation (such as the sensitivity

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[2] In subject Q, ECS was performed on 27 electrodes, which resulted in 5 ECS+ sites. ECoG-based mapping resulted in 14 ECoG+ sites. With neighbors, there were 25 ECoG + hits, which resulted in 2 true negative and 20 false positive hits. Based on these results, specificity was $2/(2+20) = 9\%$.

Table 2
Sensitivity and specificity values for each subject. The right-most column indicates the fraction of ECoG+ electrodes that were within 1.5 cm of an ECS+ electrode. Electrodes that were not stimulated were not considered for the comparisons. Sensitivity cannot be computed in subjects that did not have at least one ECoG+ site, and is reported here as not applicable (N/A).

Subj.	Sens. (%)	Spec. (%)	Within 1.5 cm (%)
A	100	81	88
E	100	63	100
G	50	86	40
H	100	72	89
I	N/A	100	N/A
J	N/A	74	N/A
L	100	32	65
M	100	50	89
N	N/A	63	N/A
O	100	81	50
Q	100	9	100
R	N/A	40	N/A
U	100	65	100
V	N/A	0	N/A
W	100	75	100
Avg.	95	59	82

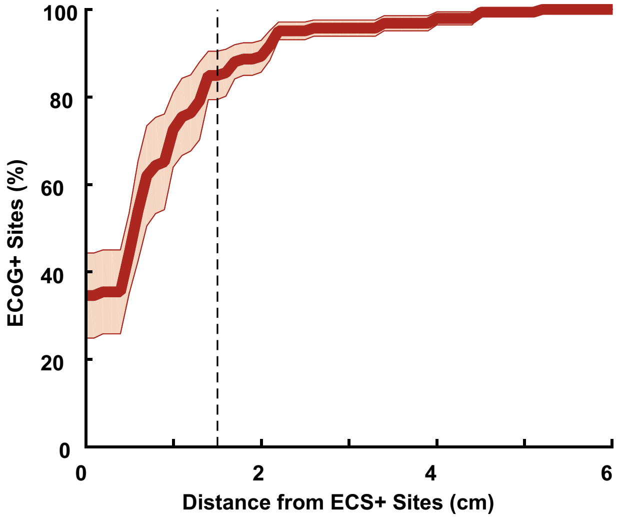

Fig. 3. Percentage of ECoG+ sites within a certain distance of ECS+ sites. The thick red line represents the fraction of ECoG+ electrodes within a certain distance of an ECS+ electrode, averaged across the subset of 10 subjects for whom ECS resulted in reliable inhibition of language function. The shaded region represents the standard error of the mean. The dashed vertical line indicates the 1.5 cm distance mark. 82% (±7.1%) of ECoG+ electrodes are within that distance of an ECS+ electrode. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and specificity metrics used here) presume that maps produced by ECS are correct and that any deviation from those maps with the use of a different method are due to shortcomings of the method being compared to ECS.

Together with the qualitative results shown in Figs. 2 and 3, the nature of the two different methods may provide clues to resolving this unsatisfactory situation: ECS-based mapping is based on a subjective, qualitative, and coarse evaluation (e.g., visual observation of the patient's behavior), whereas ECoG-based mapping is based on an objective, quantitative, and highly sensitive procedure (i.e., automated statistical evaluation by a computer algorithm). Hence, it seems plausible that ECS identifies only those locations whose stimulation produces deficits so pronounced (e.g., complete interruption of speech) that they can be readily identified during the necessarily brief evaluations during the stimulation procedure, whereas ECoG also identifies locations that are responsible for more nuanced aspects of language function. Notable in this context, it is well known that the auditory system is composed of distinct constituent functional areas that evaluate different aspects of auditory or language function such as music (Norman-Haignere et al., 2015), syntax (Blank et al., 2016), or semantics (Fedorenko et al., 2016). All of these areas can be identified by the ECoG-based method. At the same time, without application of detailed auditory and language batteries (which are impractical due to the lengthy amount of time required), the ECS-based method will fail to identify those important areas of auditory or language function. In this view, locations that produce the most substantial deficits in function are defined by the ECS-based method, and these locations are surrounded by a functional penumbra of cortex that is also involved in subtler yet still important aspects of language function. Thus, excision of ECoG+ sites that are ECS- may well produce detectable functional deficits. Indeed, a growing number of recent studies are providing initial experimental evidence supporting this view (Kojima et al., 2012, 2013; Cervenka et al., 2013; Genetti et al., 2015).

The concept of a functional penumbra identified by those ECoG+ sites that are not identified by ECS may provide the physiological basis for the empirical "1-cm rule" in functional neurosurgery. This rule is based on previous findings (Haglund et al., 1994; Ojemann and Dodrill, 1985) that excision of cortex within 1–2 cm of contacts identified by ECS greatly increases the likelihood of producing functional deficits (Hamberger, 2007). Consistent with these findings, we found that 82% of the ECoG+ contacts were within 1.5 cm (i.e., one lateral or diagonal contact in a standard grid with 10-mm spacing) of an ECS+ site. If this notion is correct, function should remain completely intact if all ECoG+ sites are spared.

This important observation notwithstanding, different types of function clearly carry different levels of importance to a patient's quality of life. The best example is non-dominant language function, which is readily identified by our ECoG-based method (see subjects A, J, M, N, O, P, S, and V Fig. 1) or by fMRI (Norman-Haignere et al., 2015; Blank et al., 2016; Binder et al., 1997; Benjamin et al., 2017). While it is increasingly clear that the non-dominant hemisphere is involved in different aspects of expressive (Cogan et al., 2014) and receptive (Chang et al., 2011) language function, there are still uncertainties about the functional significance of non-dominant receptive language areas. It does appear that it is related in part to speech prosody (Ross and Mesulam, 1979; Ross, 1981), i.e., not how a voice sounds or what its words mean, but rather how one says those words. Thus, it is quite possible that ECS-based mapping typically does not identify receptive language function on the non-dominant hemisphere simply because conventional receptive language mapping tasks only test auditory/sentence comprehension and not their affective interpretation. To complicate this interpretation, we did observe inhibition of receptive language function in non-dominant language cortex during ECS mapping (subjects A, M, O). In any event, more comprehensive ECS language testing may in theory be able to identify much more subtle aspects of receptive language, but the long duration and risks associated with ECS mapping will likely mean continued focus on testing those aspects of language function that are most important to quality of life.

Because it is critical for people to hear sounds and understand the meaning of spoken words, and presumably less important to learn about the affective context of those sounds or words, non-dominant temporal lobe is usually excised when clinically indicated (e.g., by the presence of a tumor or epileptic foci) without consideration of any language areas. Hence, the necessarily brief and coarse evaluations of language function during ECS-based mapping do provide information about the localization of those aspects of receptive language function that appear to be most useful to human functioning, and ECoG protocols that highlight only those areas still need to be developed. Design of these more specialized ECoG-based mapping batteries should be informed by the extensive literature on the functional compartmentalization of the language system. Once developed, application of those batteries should provide unprecedented utility to clinicians in their surgical planning and for informing the patient about potential functional deficits resulting from surgery. In any case, derivation of functional ECoG maps and their careful comparison to other modalities such as ECS (as performed in our study) clearly requires rigorous quantitative methods. This position is in strong opposition to a recent report (Asano and Gotman, 2016) that argued for qualitative visual inspection of gamma changes.

ECS has been the gold-standard for functional mapping for decades. It is widely accepted that application of conventional ECS methods produces specific and reliable outcomes at defined sites, and that neurosurgical resective strategies guided by this method eliminate or minimize sensorimotor and linguistic post-operative deficits (Haglund et al., 1994; Sanai et al., 2008). Despite its long history and undeniable practical utility, ECS also has clear and broadly acknowledged shortcomings. It is time-consuming and may evoke after-discharges or seizures that can reduce or eliminate its utility. Furthermore, despite its widespread and longstanding clinical usage, the technique is still not standardized, and different centers have striking inconsistencies in methodology and subsequent resection strategies (Hamberger et al., 2014). Thus, what is clearly required is not only the innovation of new methods that do not have the limitations of ECS, but also large and prospective studies that carefully evaluate the relationship of results achieved with any method with post-operative outcome. Unfortunately, clinical and practical realities have largely limited studies of mapping efficacy (including the work described here) to retrospective evaluations of a relatively limited number of patients that did not receive comprehensive post-operative neuropsychological evaluation. This situation is continuing to leave ample room for methodological debates.

5. Conclusions

In our study, we completed the largest evaluation of passive ECoG-based mapping of receptive language function to date. The results are encouraging and, perhaps even more importantly, helped us to propose a refined understanding of the basis for and interpretation of ECS- and ECoG-based results. Due to its ease-of-use, ready availability, and refined appreciation of its function described herein, it is becoming increasingly obvious that passive ECoG-based mapping will become one of the most important novel tools in presurgical functional mapping. At a growing number of medical centers, this is already the case.

Conflict of interest statement

Mr. Swift was employed by g.tec during the time of this study, and was involved in developing cortiQ, a commercial tool for mapping of cortical function.

Dr. Coon was employed by g.tec during the time of this study, and was involved in developing cortiQ, a commercial tool for mapping of cortical function.

Dr. Guger is CEO of g.tec, which is developing cortiQ, a commercial tool for mapping cortical function.

Dr. Brunner holds intellectual property for brain mapping technologies, and may derive licensing income from the same.

Dr. Bunch reports no disclosures.

Dr. Lynch reports no disclosures.

Dr. Frawley reports no disclosures.

Dr. Ritaccio holds intellectual property for brain mapping technologies, and may derive licensing income from the same.

Dr. Schalk holds intellectual property for brain mapping technologies, and may derive licensing income from the same.

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JRS performed the statistical analysis and wrote the paper.

WGC analyzed data and wrote the paper.

CG supervised the study.

PB implemented and performed the experiment, and extracted the data.

MEB performed the experiment.

TML performed the experiment.

BKF performed the experiment.

ALR wrote the paper and supervised the study.

GS designed and supervised the study, and wrote the paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.09.007.

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