HHS Public Access

Author manuscript

Epilepsy Behav. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

Epilepsy Behav. 2018 February ; 79: 26–33. doi:10.1016/j.yebeh.2017.10.044.

ECoG high-gamma modulation versus electrical stimulation for pre-surgical language mapping

Ravindra Arya, MD, DM[1], **Paul S. Horn, PhD**[1], and **Nathan E. Crone, MD**[2]

[1]Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A

[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A

Abstract

Objective—This meta-analysis compared diagnostic validity of electrocorticographic (ECoG) high-γ modulation (HGM) to electrical stimulation mapping (ESM) for pre-surgical language localization.

Methods—From a structured literature search, studies with electrode level data comparing ECoG HGM and ESM for language localization were included in the meta-analysis. Outcomes included global measures of diagnostic validity: area under the summary receiver operating characteristic (SROC) curve (AUC), and diagnostic odds ratio (DOR); as well as pooled estimates of sensitivity and specificity. Clinical and technical determinants of sensitivity/specificity were explored.

Results—Fifteen studies were included in qualitative synthesis, and 10 studies included in the meta-analysis (number of patients 1–17, mean age 10.3–53.6 years). Overt picture naming was the most commonly used task for language mapping with either method. ECoG HGM was analyzed at 50–400 Hz with different bandwidths in individual studies. For ESM, pulse duration, train duration, and maximum current varied greatly among studies. Sensitivity (0.23–0.99), specificity (0.48–0.96), and DOR (1.45–376.28) varied widely across studies. The pooled estimates are: sensitivity 0.61 (95% CI 0.44, 0.76), specificity 0.79 (95% CI 0.68, 0.88), and DOR 6.44 (95% CI 3.47, 11.94). AUC was 0.77. Results of bivariate meta-regression were limited by small samples for individual variables.

Correspondence: Ravindra Arya, Division of Neurology, E4-145, MLC 2015, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, Ohio 45229, U.S.A. Ravindra.Arya@cchmc.org; P: (513) 636-4222; F: (513) 636-1888.

Contributions: Study concept, design, literature search, data extraction: NEC, RA; data analysis: RA, PSH; first draft: RA; critical review: NEC, PSH. All authors approve the final version.

Disclosure(s): Research reported in this paper was supported by NINDS of the National Institutes of Health (NIH) under award number R01NS091139 (PI: NEC). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. There are no other conflicts to disclose.

Conclusion—ECoG HGM is a specific but not sensitive method for language localization compared to gold-standard ESM. Given the pooled DOR of 6.44 and AUC of 0.77, ECoG HGM can fairly reliably ascertain electrodes overlying ESM cortical language sites.

Keywords

Functional brain mapping; Language localization; Epilepsy surgery

1. INTRODUCTION

To ensure safe and effective resective neurosurgery for epilepsy, tumors, and other brain lesions, it is often necessary to determine the functional localization of language cortex in individual patients. The conventional method of extra-operative electrical stimulation mapping (ESM) involves stimulation of implanted intracranial electrodes and observation for behavioral effects. ESM is associated with risks of after-discharges, seizures, and pain, which can all interfere with comprehensive mapping [1, 2]. There is also evidence for language thresholds to exceed after-discharge thresholds particularly in younger children [3]. Moreover, because it must be done sequentially for electrode pairs, ESM is time consuming, effectively limiting the number of sites that can be tested. The neurophysiological validity of stimulation-induced “all-or-none” interference with elementary language tasks to faithfully capture brain language representation is also questionable [4]. Hence, an alternative approach for functional localization has emerged, based on task-related modulation in electrocorticograph (ECoG) spectra [5]. This approach has usually focused on power modulations in the high-γ (typically >40 Hz) band, which have shown good correlation with neural firing rates and blood oxygen-level dependent response [6]. ECoG high-γ modulation (HGM) has been consistently observed during several language tasks with favorable spatial-temporal profile [7, 8]. However, clinical validation of ECoG HGM mapping against ESM is limited to small samples with variable results. This has frequently raised concerns whether ECoG HGM should be adopted in routine clinical practice, either as a supplement or replacement for ESM. Hence, this meta-analysis was performed to obtain pooled estimates of the diagnostic validity of ECoG HGM compared to ESM for pre-surgical language localization and to explore the sources of variability among the studies.

2. METHODS

2.1 Literature search

Electronic databases including PubMed, EMBASE (all resources), and Cochrane library (all registers) were systematically searched on December 16, 2016 for articles in English, with appropriate keywords related to functional mapping, high-frequency oscillations, and neurosurgery (Table e1). Studies comparing language localization with ECoG HGM and ESM were eligible for inclusion. For this study, we defined γ-band as ≥50 Hz [9, 10]. Studies which reported neither sensitivity/specificity, nor sufficient electrode level data to allow their calculation, were excluded. Studies where ESM did not interfere with language function, or where authors analyzed HGM in arbitrarily spatially restricted electrodes, were also excluded.

2.2 Data extraction

Following variables were extracted from the included studies: number of patients, mean age, native language, sample criteria, tasks used for ECoG HGM and ESM, frequency band for ECoG HGM analysis, ESM settings (pulse frequency, pulse duration, stimulus train duration, maximum stimulation current), and criterion for scoring ESM positive electrodes. Electrode level data (i.e. number of electrodes positive and negative for language by ECoG HGM and ESM respectively) were extracted and used for meta-analysis from studies which provided this detail; otherwise, reported sensitivity/specificity were extracted. Some of the studies reported electrode data for multiple subgroups based on implanted hemisphere, tasks used, or definition of language positive sites. Only one representative subgroup was included per study in the meta-analysis, since the subgroups were unlikely to be mutually independent. Studies which did not report electrode level data were reviewed but could not be included in the meta-analysis.

2.3 Outcomes

The primary outcome measure was the area under the summary receiver operating characteristic (SROC) curve (AUC), which represents a global measure of diagnostic validity from pooled data. Other outcomes included pooled estimates of diagnostic odds ratio (DOR), sensitivity, specificity, and metrics representing heterogeneity in the data. Determinants of sensitivity/specificity were also explored including mean age of patients, native language (English/others), minimum and maximum frequencies of the bandwidth used for ECoG HGM analysis, and pulse duration and maximum current strength used for ESM.

2.4 Statistical analysis

The meta-analysis of ESM and ECoG HGM comparisons presented unique challenges, since each study contributed multiple patients, each having multiple electrodes for eventual analysis. These electrodes cannot be regarded as independent observations since they are nested by patients in each study, necessitating a multilevel approach. Further, the sensitivity and specificity of each study is correlated and requires a bivariate model for their joint distribution. Due to these considerations, sensitivity, specificity, and DOR for individual studies was first calculated, along with 95% confidence interval (CI), from electrode data. Equality of sensitivities and specificities across studies were tested using χ^2 test to explore heterogeneity in the data. Then, pooled estimates of sensitivity, specificity, and DOR were obtained with bivariate random effects meta-analysis using the restricted maximum likelihood method. AUC was estimated from a hierarchical SROC curve obtained by modeling its slope in the logit space as the geometric mean of slopes of 2 regression lines, logit(sensitivity) on logit(1 – specificity) and vice versa [11]. This ensures the symmetry of the SROC curve with respect to sensitivity and specificity and also accounts for potential differences in the precision of the estimates from included studies. Pooled DOR was obtained using DerSimonian and Laird (DSL) estimator, along with Higgin's I^2 statistic which represents the proportion of observed variance from the "true" heterogeneity in effect size [12]. The DSL method incorporates study-specific heterogeneities using inverse variance approach to adjust weight assigned to each study. A bi-variate meta-regression was

performed to explore determinants of the joint distribution of sensitivity and false positive rate (FPR = 1 – specificity) using the linear mixed model described by Reitsma et. al. [13]. Odds ratios (OR) with 95% CI were obtained for sensitivity and FPR for all covariates using inverse logit transformation on the fitted models. This is essentially an extension of random effects approach and assumes the (logit transformed) sensitivities and specificities of the analyzed studies to be approximately normally distributed with the variability resulting from unmeasured differences in the study population or test performance. This framework also incorporates possible correlation between sensitivity and specificity, sampling error, and provision for including covariates. All analyses were performed using the "MADA" library in R [14].

3. RESULTS

Fifteen studies were included, having 1 to 17 patients, with mean age varying from 10.3 to 53.6 years (Table 1) [15–29]. Six of the studies included native speakers of languages other than English. Overt picture naming was the most common task used both for ECoG HGM as well as ESM; however, a multitude of tasks/task-combinations were used for language mapping (Tables 1, 3). The frequency band for ECoG power modulation varied from 50 to 400 Hz with different bandwidths. The pulse frequency used for ESM was identical across the studies at 50 Hz, but the pulse duration (200–500 us), train duration (2–10 s), and maximum current (5–15 mA) varied greatly. Five studies did not provide electrode level data, allowing only 10 studies to be included in the meta-analysis (Fig. 1) [15–17, 19–22, 25].

3.1 Diagnostic accuracy meta-analysis

Sensitivity (0.23–0.99), specificity (0.48–0.96), and DOR (1.45–376.28) varied widely across individual studies (Fig. 2) [17, 22, 25]. For studies that provided electrode level data, this was also substantiated by the test for equality of sensitivity and specificity which showed significant heterogeneity ($p<0.0001$ for both sensitivity and specificity), and the large confidence intervals around these data points (Fig. 3). The pooled estimates were: sensitivity 0.61 (95% CI 0.44, 0.76) and specificity 0.79 (95% CI 0.68, 0.88). The pooled DSL estimate for DOR was found to be 6.44 (95% CI 3.47, 11.94) with low heterogeneity ($I^2 = 23.1\%$) [30]. The AUC was estimated to be 0.77. The pooled estimates along with confidence and prediction ellipsoids for the joint distribution and SROC curve are shown in Figure 4.

3.2 Meta-regression

A bivariate meta-regression for the joint distribution of sensitivity and FPR found maximum current used for ESM (OR 39.31, 95% CI 4.02, 384.25, p = 0.001) to significantly determine sensitivity. Also, studies including speakers of languages other than English had significantly higher specificity (lower FPR, OR 0.06, 95% CI 0.01, 0.28, p = 0.001) compared to studies of English speakers (Table 2).

4. DISCUSSION

This meta-analysis showed that ECoG HGM is a specific (0.79, 95% CI 0.68, 0.88) but not sensitive (0.61, 95% CI 0.44, 0.76) modality for language localization compared to ESM as the current clinical gold-standard. Note that CI around the pooled estimate included 0.5 for sensitivity but not specificity. Pooled DOR of 6.44 (95% CI 3.47, 11.93) indicates that electrode sites with HGM, compared to those without, have a 6.44 times greater odds of being classified as ESM-defined language cortex. Given this pooled DOR and an AUC of 0.77 from SROC curve, ECoG HGM was a good binary classifier of electrodes overlying language cortex (Fig. 4). Thus, with good specificity and DOR, ECoG HGM can be relied upon to ascertain electrodes which are likely to be ESM− for language, but probably not otherwise.

The data showed significant heterogeneity as evident from large confidence ellipsoids around study-specific estimates (Fig. 3), and tests for equality of sensitivity and specificity across studies. However, the meta-regression performed to explore sources of this heterogeneity was not informative, in our opinion (Table 2). The maximum current used for ESM was found to significantly determine sensitivity, and the specificity of studies including non-English speaking patients was significantly higher than that of studies including native English speakers. However, it is possible that these findings represent aberrations due to data architecture, and lack physiological basis. A majority of the studies (n = 9) used 10–15 mA as the maximum current for ESM. However, one study which reported 100% sensitivity, performed ESM at only up to 5 mA (Fig. 5) [17]. Similarly, the effect of native language was driven by 2 studies only. Hence, the observed statistical significance in the regression analysis could have been due to the small number of data points and the effects of these outliers.

Additional potential sources of variability in the sensitivity/specificity of ECoG HGM compared to ESM, include the methods for performing, analyzing, and interpreting these techniques. Regarding ESM, although the pulse frequency was consistent across the studies, there was variability in the pulse duration, train duration, and maximum current used. These variables affect the ability to perform sufficient trials of a given language task during stimulations, and to observe for interference with task performance. For trial-based tasks like picture naming, the train duration should be sufficient to allow the patient to see and name at least 2–4 pictures during stimulation, to permit observation for consistent interference. Also, it is known that the current strength required to cause interference with language tasks, is a function of age, after-discharge thresholds, and prior stimulation [31, 32]. Especially in children, a higher current strength, often above the after-discharge threshold, is required for interference with language task(s) [1, 3, 33]. In fact, the optimal current strength for ESM is not well-established, and varies across centers. Some evidence suggests that ESM may relatively poorly localize language cortex in young children compared to older individuals [33]. However, lack of separate pediatric electrode-level data in studies including both children and adults, precludes a subgroup analysis for HGM and ESM diagnostic comparison (Table 3).

Further, there was no uniformity in the language tasks used for ESM (Tables 1, 3). Studies on ESM have shown that stimulation of different regions of the cortex can produce task-specific interference. For example, ESM in peri-sylvian cortex is known to interfere with orofacial motor sequencing, phoneme identification, and automatic speech tasks [34, 35]. Whereas, repetition tasks, visual naming, and auditory naming sites have been identified in mid-to-posterior superior temporal gyrus, posterior inferior frontal gyrus, and adjacent regions [35, 36]. Limited evidence suggests further variability in verb generation sites including frontal lobe (anterior to visual naming sites), and temporo-parietal cortex [37].

The scoring of electrodes as ESM+ for language was also variable across studies. It is important to note that while ESM is often performed between electrode pairs, HGM analysis is based on referential ECoG recordings which yield estimates of activation at individual electrodes. In clinical practice, it is common to score an electrode as ESM+ only if stimulation consistently interferes with language task in two or more tested pairs including that electrode. For electrodes tested only in a single pair, it is customary, at least in our centers, to score them same as the pair. While many studies have conformed to this clinical practice [16, 18, 26], others have used the more liberal “next-neighbor” approach of scoring all electrodes surrounding the one with language interference as being positive by ESM [17, 19]. A similar approach has been used in a study demonstrating the clinical utility of ESM [38].

Methodological variability was even greater for language mapping with ECoG HGM, which was performed in most centers purely for research purposes. There was almost no uniformity in the equipment and computational methods used for signal acquisition, pre-processing, and analysis. Although a majority of studies averaged the power change over a number of trials of a given language task [17–20, 23, 26, 28], others used block designs based on signal modeling for real-time identification and event detection (SIGFRIED) algorithm of BCI2000 [15, 21, 24], or custom methods specific to their labs [22, 29]. Channels with excessive artifact or epileptiform activity also confound power estimation for ECoG HGM signal analysis, particularly with trial-averaging. However, many of the studies have specified removing noisy channels before re-referencing to the common average [15–18, 24, 27]. The frequency bandwidth used for analysis of task-related power modulations, and the language tasks themselves, varied widely across studies (Tables 1, 3). The criteria for scoring an electrode as positive for language-related HGM were also inconsistent. Some studies used pre-specified statistical cut-offs, whereas others arbitrarily chose electrodes based on location or those with highest power differential compared to baseline [15, 16, 23, 26, 27]. These factors along with the variability in electrode coverage in individual patients, and potential reorganization of brain networks due to chronic epilepsy, made evidence synthesis and interpretation of pooled data very challenging.

Like any other evidence synthesis, we could only attempt to reconcile disparate studies, but could not improve upon the heterogeneous source data. Several eligible studies did not provide electrode level data, thus precluding them from meta-analysis. Many of those who did provide such data, analyzed it in multiple different subgroups based on anatomic location of analyzed electrodes, tasks used for ESM/ECoG HGM, or criteria for scoring ESM+ electrodes, while we could include only one subgroup per study (Table 3). Further,

individual patients in each study contributed multiple electrodes towards the meta-analysis, whereas we had to regard the patients as independent observations. There is a lack of mathematical methods to model such a multilevel nested analysis for diagnostic accuracy comparisons [11]. Hence, our pooled estimates should only be regarded as suggestive of general trends.

Compared to ESM, ECoG HGM has a number of potential advantages for clinical practice. Because it is based on passive recordings, ECoG HGM carries no risk of pain, after-discharges, or stimulated seizures, and it can be used to rapidly, and less tediously, survey all electrodes simultaneously at the bedside. However, the results of our meta-analysis suggest that ECoG HGM is a specific, but not sensitive, classifier of ESM language sites. If one assumes that ESM provides the ground truth for cortical language representation and accurately predicts the outcome of cortical resection, our results would argue that ECoG HGM cannot totally replace ESM. Rather, ECoG HGM can be used to predict ESM− sites with good specificity and thus prioritize other sites for ESM before they are resected, but it cannot rule out function at a site or declare it safe for resection without also testing it with ESM. This conclusion is somewhat counterintuitive given that ECoG HGM being an activation modality, potentially shows all sites participating in a task, while ESM, which supposedly creates a transient lesion, should detect the subset of those sites which are critical for the task performance.

Although the studies reviewed here all used ESM as the gold-standard, there are a number of reasons to question this assumption. There is limited data about the geometry of current spread in brain tissue after stimulation of subdural electrodes [39], and important knowledge gaps remain about the physiological and physical determinants of language response inhibition thresholds during ESM [3]. Also, remote after-discharges noted during and after ESM suggest that electrical stimulation of a localized area of cortex can have distant neurophysiologic effects mediated by preferentially connected pathways [31, 40]. These factors may be partly responsible for the imperfect correlation between ESM findings and long-term post-operative language outcomes [4, 41, 42].

5. CONCLUSION

Our meta-analysis underscored the heterogeneity in performing, analyzing, and interpreting ECoG HGM language mapping in available studies. If ECoG HGM is to provide a potentially safer and more patient-friendly modality for language mapping in future, then there is a need for uniform methods for signal acquisition, processing, analysis, and interpretation. Most importantly, the results of ECoG HGM should be validated against long-term post-operative language outcomes, preferably in larger, more homogeneous patient populations. Since ECoG HGM simultaneously generates information about all implanted electrodes compared to ESM which is usually limited to a subset of electrodes, larger sample studies will be needed to generate more reliable estimates of predictive values that can guide clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

RA wishes to acknowledge Dr. Susan T. Herman of Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, for support through the American Epilepsy Society's EpiPORT program; Dr. Phillip Doebler of Technical University, Dortmund, Germany, for help with the MADA package in R; and Dr. Yujing Wang of Johns Hopkins University for sharing raw data from her publication.

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HIGHLIGHTS

- ECoG high-γ modulation is a specific method for pre-surgical language localization
- It can reliably ascertain language sites localized by electrical stimulation mapping
- It can be a potentially safer technique for language mapping in selected patients

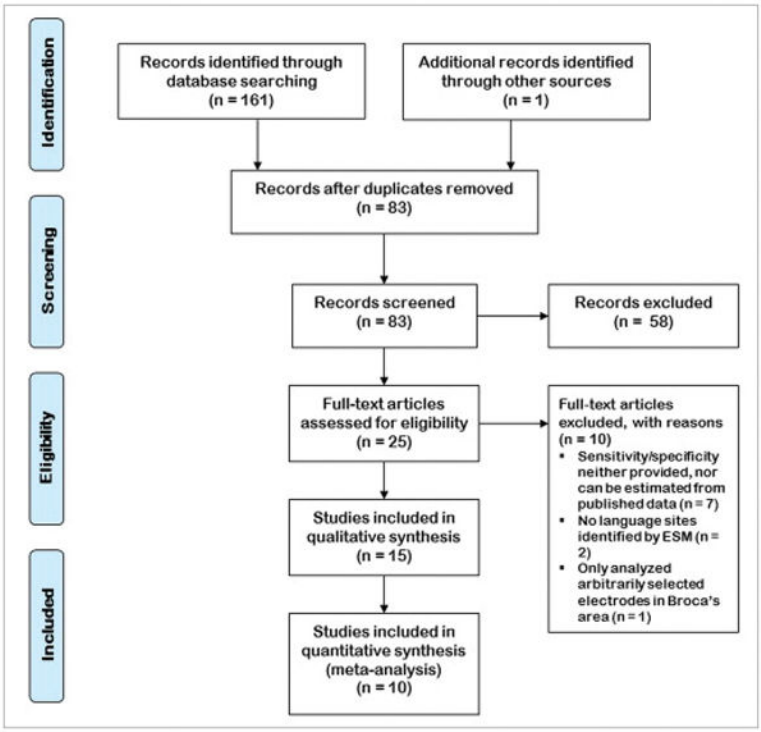

Figure 1.
The PRISMA flow diagram

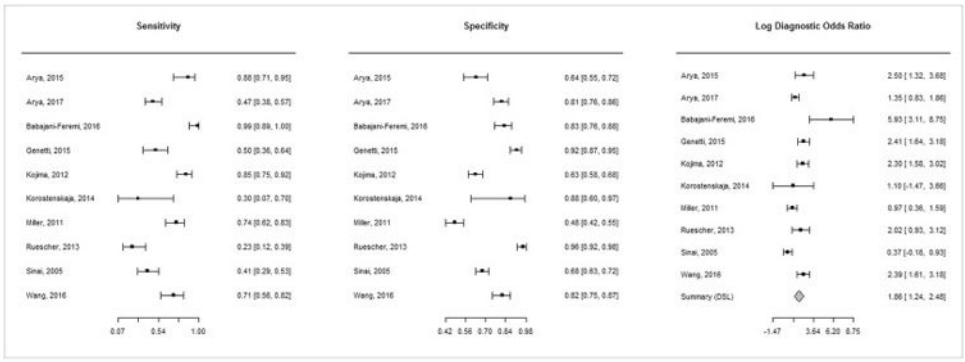

Figure 2.

Forest plots of sensitivity, specificity, and diagnostic odds ratio (DOR) showing study specific estimates with 95% confidence intervals for these metrics.

The estimates for DOR are on a logarithmic scale. Since the sensitivity/specificity pairs from all studies are correlated, separate pooled estimates are not calculated for them. Instead, a pooled estimate for DOR is obtained.

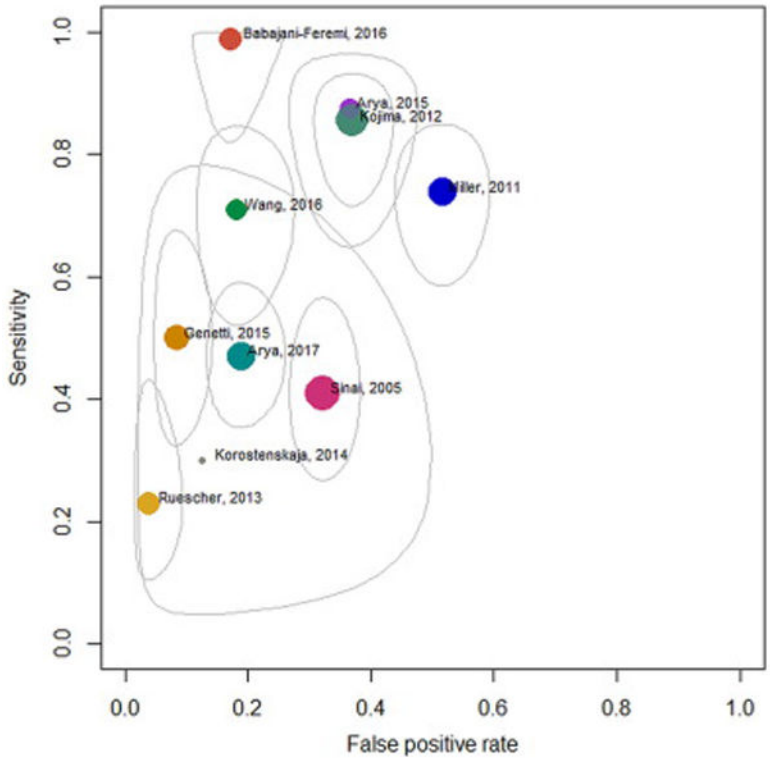

Figure 3.

Confidence ellipsoids for the uncertainty in the pair of sensitivity and false positive rate Confidence regions for the study specific paired estimates of sensitivity and false positive rate (colored bubble), plotted in the receiver operating characteristic (ROC) space. The size of the bubble is proportional to the total number or electrodes in the study.

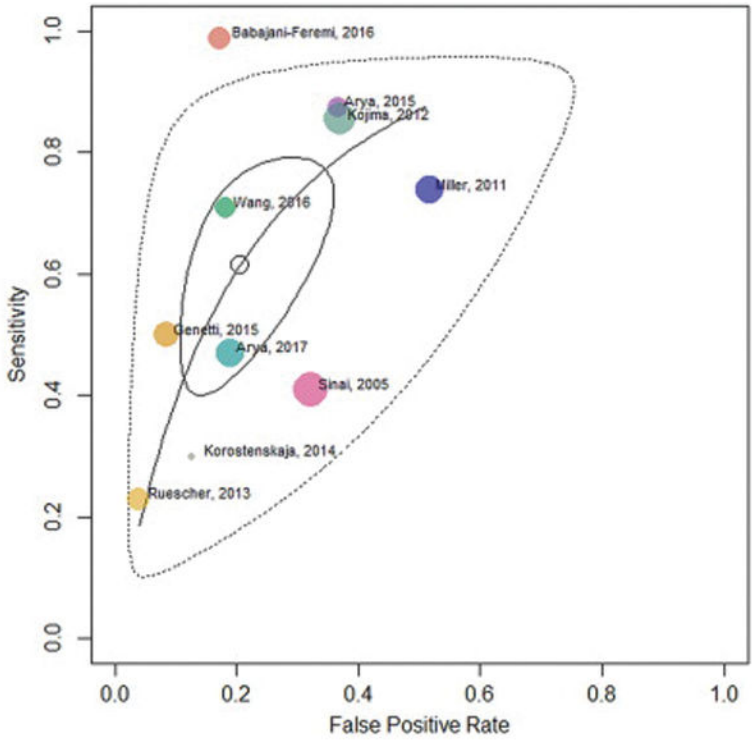

Figure 4.

Summary Receiver Operating Characteristic (SROC) curve

SROC curve is shown with pooled estimate (open circle), 95% confidence region (solid closed curve), and 95% prediction region (dotted closed curve). This curve is obtained by modeling its slope in the logit space as the geometric mean of the slopes of the two regression lines, logit (sensitivity) on logit (false positive rate) and vice versa (Rutter-Gatsonis Hierarchical SROC). Study specific estimates (colored bubbles) are also shown. The size of the bubble is proportional to the total number or electrodes in the study.

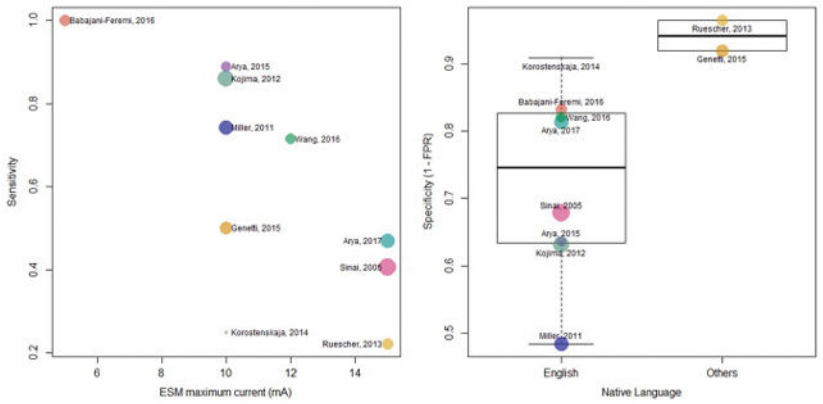

Figure 5.

Determinants of pairs of sensitivity and false positive rate on bi-variate meta-regression

Bi-variate meta-regression showed maximum frequency used for electrocorticographic (ECoG) high-γ modulation (HGM), and maximum current used for electrical stimulation mapping (ESM) to be significant determinants of sensitivity (upper panel). Studies including native speakers of languages other than English showed significantly lower sensitivity and higher specificity (lower panel).

TABLE 1

Studies included in qualitative and quantitative (*) synthesis for comparison of electrical stimulation mapping (ESM) and electrocorticographic (ECoG) high-γ modulation for extra-operative language localization

Study	n	Age (years, mean ± SD)	Native language	Sample criteria	ECoG task(s)	Frequency band (Hz) for ECoG HGM	ECoG signal processing	ESM task(s)	ESM pulse duration, train duration, maximum current	ESM+ definition	Sensitivity	Specificity
Arya, 2015*^	7	10.3 ± 4.1	English	Excluded those unable to converse	Conversational Speech	70–116	Custom block design based on SIGFRIED (500 ms windows)	Picture naming	500 μs, 5s, 10 mA	Naming and/or oral motor deficits	0.89	0.63
Arya, 2017*^	17	11.3 ± 4.4	English	Included patients able to name pictures	Overt picture naming	70–116	Custom block design based on SIGFRIED (500 ms windows)	Picture naming	500 μs, 5 s, 10–15 mA	Naming and/or oral motor deficits	0.47	0.81
Babajani- Feremi, 2016*	9	23 ± 8	English	LH language dominance; No known frontal lobe pathology that could affect language representation	Overt object naming	50–119	TPC to identify clusters of bins spanning ≥20 Hz and 150 ms within [0 3]s time window	Sentence reading; comprehension of spoken sentences; sentence repetition; confrontation naming; modified token test	500 μs, 3–5 s, 5 mA	Speech arrest or disruption, not accompanied by positive motor signs	1.00	0.83
Bauer, 2013^	8	36.1 ± 7.8	Dutch	Age >12 years; no language/other major cognitive impairment; LH language on IAT	Speaking (retrospective 90 s epochs)	65–95	TPC	Object/picture naming	NA, 4–7s, 10 mA	Speech arrest/disruption	0.22	0.82
Genetti, 2015*	12	23.1 ± 13	French German, English^		Semantic congruency decision	70–160	TPC using 80 ms sliding Hamming windows with 87.5% overlap ratio	Automatic speech (counting or naming)	300 μs, 2–5 s, 10 mA		0.50	0.92
Kojima, 2012*^	13	16.3 ± 8.2		LH language by IAT; Excluded “massive” MCD (peri-Sylvian, peri-Rolandic, hemispheric)	Response to an auditory question	50–120	TPC	Response to auditory question(s), picture naming, counting, reciting alphabet	300 μs, 5–10 s, 9 mA	Naming difficulty OR mouth/throat sensorimotor symptoms	0.91	0.61
Korostenskaja, 2014*	1	13			Picture naming, story listening	60–170	Custom block design based on SIGFRIED (500 ms windows)	Picture naming	200 μs, 5 s, 10 mA		0.25	0.91

Study	n	Age (years, mean ± SD)	Native language	Sample criteria	ECoG task(s)	Frequency band (Hz) for ECoG HGM	ECoG signal processing	ESM task(s)	ESM pulse duration, train duration, maximum current	ESM+ definition	Sensitivity	Specificity
Miller, 2011*[^]	7	27.3 ± 9			Verb generation	76–200	Custom method based on BCI2000 using 80 ms windows with 40 ms overlap	Verb generation	NA, 3 s, 10 mA		0.74	0.48
Mooij, 2016	9	30.6 ± 10.9	Dutch	LH or bilateral language by IAT/fMRI	Story and music listening	65–95	Custom method with γ-band time- domain signal reconstruction and discriminant analysis	Picture naming	200 μs, 4–7 s, 10 mA		0.35	0.93
Ogawa, 2017[^]	7	43.6 ± 12.6	Japanese	Brain tumors in language dominant hemisphere	Picture Naming	60–170	Custom method using a variance metric (R^2) for task-related increase in γ-power	Sentence repetition, picture naming, word reading	500 μs, NA, 15 mA		0.90	0.90
Ruescher, 2013*[^]	3	43.3 ± 4.9	German		Conversational speech	60–400	TPC (500 ms window)	Battery including reading, counting, object naming, command execution, token test, sentence repetition	250 μs, 10 s, 15 mA	Oral motor interference	0.22	0.97
Sinai, 2005*[^]	13	33.8 ± 11.2		LH language dominance, IQ> 80, no language impairment	Picture Naming	80–100	TPC with mixed effects model (100 ms epochs with 50% overlap)	Picture naming, sentence comprehension (modified token test), paragraph reading, spontaneous speech	300 μs, 1–5 s, 15 mA	Naming and/or oral motor deficits	0.43	0.84
Tamura, 2016	4	53.6 ± 17.3	Japanese	Tumor(s) involving dominant frontal/ temporal lobes	Story listening	80–160	TPC	Spontaneous speech, word repetition, picture naming	300 μs, NA, 15 mA	Speech arrest/aphasia	0.94	0.95
Towle, 2008	12	19.8 ± 8.9		Drug-resistant epilepsy	Word repetition, new word identification, conversation	70–100	TPC		300 μs, 2–10 s, 10 mA		0.63	0.57
Wang, 2016*[^]	7	36.4 ± 20	English		Picture naming, word repetititon	70–110	Trial-averaged or single trial amplitude change		NA, NA, 12 mA		0.70	0.84

(ECoG electro-corticographic, ESM electrical stimulation mapping, IQ intelligence quotient, fMRI functional magnetic resonance imaging, IAT intra-carotid amobarbital test [Wada test], LH left hemisphere, MCD malformations of cortical development, n number of patients, NA not available, RH right hemisphere, SD standard deviation, SIGFRIED signal modeling for real-time identification and event detection, TPC Trial-averaged Power Comparison (between task and baseline),

^ these studies include other subgroups as well and only one representative subgroup is included in this table, for other subgroups see table 3).

TABLE 2

Bi-variate meta-regression

		Sensitivity		FPR	
Co-variate	**Included Studies [References]**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Mean age (years)	15 [15–29]	4.17 (0.75, 23.03)	0.194	0.51 (0.11, 2.49)	0.315
Native language (Non English vs. English)	10 [15–19, 23–25, 27, 29]	0.55 (0.05, 5.59)	0.083	0.06 (0.01, 0.28)	0.001*
ECoG bandwidth lower bound (Hz)	15 [15–29]	18.96 (0.13, 2783.28)	0.317	0.04 (0.00, 3.43)	0.398
ECoG bandwidth upper bound (Hz)	15 [15–29]	4.75 (1.20, 18.73)	0.078	0.73 (0.22, 2.35)	0.054
ESM maximum current (mA)	15 [15–29]	39.31 (4.02, 384.25)	0.001*	0.45 (0.03, 6.82)	0.616
ESM pulse duration (ms)	12 [15–17, 19–21, 23–28]	0.13 (0.01, 2.50)	0.087	0.07 (0.01, 0.75)	0.325

(Bivariate random effects models were fitted to the pairs of transformed sensitivities ($Sensitivity_t$) and false positive rates (FPR_t): ($Sensitivity_t$, FPR_t) = $ax + b$, where: a = slope, b = intercept, and x = the covariate.

The transformation used was: $x \longmapsto t_a(x)$: = $a \log x - (2 - a) \log (1 - x)$

Note that for $\alpha = 1$, the logit transformation results. Hence, the odds ratios [OR] were obtained by inverse logit transformation, and represent the proportional gain in sensitivity or FPR per unit change in the covariate, for continuous variables. CI confidence interval, ECoG electrocorticographic, ESM electrical stimulation mapping, *$p \leq 0.05$)

TABLE 3

Subgroups other than those included in meta-analysis for studies that analyzed outcomes in multiple different groups based on criteria for defining electrodes overlying language sites on ESM, tasks used for language mapping, and brain lobes.

Study	Criteria for subgroups	Subgroups	Sensitivity	Specificity
Arya, 2015	Definition of ESM+	Only naming deficits	0.83	0.63
		Only oral motor	1.00	0.69
		Either	0.89	0.63
Arya, 2017	Hemisphere, definition of ESM+, task (overt or covert) used for ECoG HGM	LH, overt, ESM+ either naming/oral motor	0.47	0.81
		LH, overt, ESM+ only naming	0.40	0.76
		LH, covert, ESM+ either naming/oral motor	0.14	0.91
		LH, covert, ESM+ only naming	0.05	0.87
		RH, overt, ESM+ only oral motor	0.44	0.81
		RH, overt, ESM+ only oral motor	0.20	0.96
Bauer, 2013	Task used for ECoG HGM	Speaking (retrospective 90 s epochs)	0.22	0.82
		Listening (retrospective 90 s epochs)	0.17	0.83
		Verb generation (overt = 6, covert = 1)	0.16	0.88
		Picture naming	0.21	0.9
Kojima, 2012	Brain lobe	Left temporal lobe	0.91	0.61
		Left frontal lobe	0.83	0.64
Miller, 2011	Task used for ESM	Noun reading	0.89	0.66
		Verb generation	0.74	0.48
Ogawa, 2017	Task used for ECoG HGM	Picture naming	0.90	0.90
		Word reading (Kanji, Hiragana)	0.89	0.89
Ruescher, 2013	Definition of ESM+	Only oral motor	0.22	0.97
		Only speech difficulties	0.00	0.94
Sinai, 2005	Definition of ESM+	Only naming	0.38	0.78
		Oral motor	0.46	0.81
		Either	0.43	0.84
Wang, 2016	Task used for ECoG HGM	Picture naming	0.63	0.81
		Word repetition	0.76	0.86

Study	Criteria for subgroups	Subgroups	Sensitivity	Specificity
		Overall	0.70	0.84

(ECoG electro-corticography; ESM electrical stimulation mapping; HGM high-gamma modulation; LH left hemisphere; RH right hemisphere)