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ECoG high-gamma modulation versus electrical stimulation for presurgical language mapping

Ravindra Arya [a,*], Paul S. Horn [a], Nathan E. Crone [b]

[a] Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Objective: This meta-analysis compared diagnostic validity of electrocorticographic (ECoG) high-γ modulation (HGM) with electrical stimulation mapping (ESM) for presurgical 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. Electrocorticographic high-γ modulation 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). Area under the SROC curve was 0.77. Results of bivariate meta-regression were limited by small samples for individual variables.

Conclusion: Electrocorticographic high-γ modulation is a specific but not sensitive method for language localization compared with 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.

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 extraoperative electrical stimulation mapping (ESM) involves stimulation of implanted intracranial electrodes and observation for behavioral effects. Electrical stimulation mapping 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-discharges 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]. Electrocorticographic 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 presurgical language localization and to explore the sources of variability among the studies.

* Corresponding author at: Division of Neurology, E4-145, MLC 2015, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA.
E-mail address: Ravindra.Arya@cchmc.org (R. Arya).

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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, and 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 within 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 were 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. Area under the curve 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 bivariate 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 and 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 μs), 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 Fig. 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 with 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 with 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)