Electrical stimulation mapping of language with stereo-EEG

Ravindra Arya [a,b,*], Brian Ervin [a,c], Jonathan Dudley [d], Jason Buroker [a,e], Leonid Rozhkov [a], Craig Scholle [a], Paul S. Horn [a], Jennifer Vannest [b,d], Anna W. Byars [a,b], James L. Leach [f], Francesco T. Mangano [b,g], Hansel M. Greiner [a,b], Katherine D. Holland [a,b], Tracy A. Glauser [a,b]

[a] Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[c] Department of Electrical Engineering and Computing Systems, University of Cincinnati, Cincinnati, OH, USA
[d] Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[e] Division of Clinical Engineering, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[f] Division of Pediatric Neuro-radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[g] Division of Pediatric Neurosurgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

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ABSTRACT

Objective: We prospectively validated stereo-electroencephalography (EEG) electrical stimulation mapping (ESM) of language against a reference standard of meta-analytic functional magnetic resonance imaging (fMRI) framework (Neurosynth).
Methods: Language ESM was performed using 50 Hz, biphasic, bipolar, stimulation at 1–8 mA, with a picture naming task. Electrode contacts (ECs) were scored as ESM+ if ESM interfered with speech/language function. For each patient, presurgical MRI was transformed to a standard space and coregistered with computed tomographic (CT) scan to obtain EC locations. After whole-brain parcellation, this fused image data were intersected with three-dimensional language fMRI (Neurosynth), and each EC was classified as lying within/outside the fMRI language parcel. Diagnostic odds ratio (DOR) and other indices were estimated. Current thresholds for language inhibition and after-discharges (ADs) were analyzed using multivariable linear mixed models.
Results: In 10 patients (5 females), aged 5.4–21.2 years, speech/language inhibition was noted with ESM on 87/304 (29%) ECs. Stereo-EEG language ESM was a valid classifier of fMRI (Neurosynth) language sites (DOR: 9.02, p < 0.0001), with high specificity (0.87) but poor sensitivity (0.57). Similar diagnostic indices were seen for ECs in frontal or posterior regions, and gray or white matter.
Language threshold (3.1 ± 1.5 mA) was lower than AD threshold (4.0 ± 2.0 mA, p = 0.0001). Language and AD thresholds decreased with age and intelligence quotient. Electrical stimulation mapping triggered seizures/auras represented patients' habitual semiology with 1 Hz stimulation.
Conclusions: Stereo-EEG ESM can reliably identify cerebral parcels with/without language function but may under detect all language sites. We suggest a 50-Hz stimulation protocol for language ESM with stereo-EEG.

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1. Introduction

Intracranial EEG evaluation with stereotactic depth electrodes (stereo-EEG) is rapidly emerging as an alternative to subdural electrodes for localization of the seizure-onset zone (SOZ) [1–3]. Although the technique of stereo-EEG was developed in 1960s, advances in neuroimaging and robotic assistance have fostered this renewed interest. Safe and effective epilepsy surgery also requires defining the anatomy of cerebral regions serving critical functions, and their relationship to SOZ. With subdural grids, electrical stimulation mapping (ESM) has been regarded as the clinical standard for localizing language cortex [4]. However, with stereo-EEG, there is a paucity of data on the diagnostic validity of ESM for language localization. Experience with stereo-EEG language ESM is limited to descriptive reports without any comparative validation [5–7]. Recent guidelines on stereo-EEG also do not provide any recommendations for language localization [8]. To address this knowledge gap, we performed a prospective study to validate language ESM with stereo-EEG against a reference standard of functional language neuroanatomy derived from a meta-analytic 3D functional magnetic resonance imaging (fMRI) framework. The primary

hypothesis was that speech/language interference during ESM with stereo-EEG will be a valid classifier of electrode contacts (ECs) lying within language parcels in both gray and white matter, as defined by meta-analytic fMRI framework. We also studied determinants of current thresholds for language inhibition and after-discharges (ADs) to better evaluate the safety of ESM with stereo-EEG.

2. Methods

2.1. Participants

All patients undergoing stereo-EEG evaluation were eligible for inclusion. The decision to perform language ESM was individualized based on proximity of SOZ to the canonical language regions, as assessed during noninvasive presurgical evaluation. The sequence and number of ECs stimulated for language ESM were decided by the clinical team. We excluded patients who did not undergo language ESM. The study was approved by the institutional review board (#2017-4025). Informed consent was obtained from all patients aged ≥18 years. Parental permission was obtained for all other patients, including assent from competent patients aged 11–17 years.

2.2. Language ESM

These patients were implanted with 0.86 mm stereotactic depth electrodes having 2.41 mm platinum contacts (Ad-Tech, Oak Creek, WI), for chronic invasive monitoring. Based on our experience of language ESM with subdural electrodes, we used high-frequency stimulation protocol with stereo-EEG in all patients (Table 1) [9]. We used bipolar, biphasic, square-wave stimulation, with 1 mA initial current. The current strength was increased by 0.5–2 mA up to a maximum of 8 mA, until a functional response, evolving ADs, or a seizure occurred. We typically stimulated an electrode from the deepest to the most superficial contact, because of the concern that prior stimulation of cortex could possibly render the white matter contact(s) refractory to stimulation because of preferential orthodromic propagation of stimulation [6]. We did not stimulate EC pairs on different electrodes. Because there is no consensus on the technique of language ESM with stereo-EEG, we deferred the decision to additionally perform low-frequency stimulation in a given patient to the attending clinician.

A visual naming task was used, with a series of pictures of common objects shown to the patient, after requesting her/him to name them aloud. A trial run was performed before ESM, to exclude the pictures that the patient was unable to name. Premedication with fosphenytoin was used before ESM [10]. Each EC was tested in 2 pairs and was scored as showing a language response (ESM +), only if speech/language interference was seen during both the stimulations. However, the ECs lying at the ends of the electrodes (deepest and the most superficial) could be tested in only one pair and were scored according to the response during that single test. As speech/language errors during ESM could be due to interference with cognitive (aphasia, paraphasic errors), sensorimotor, or memory (amnestic anomia) aspects of brain function; and it is sometimes not possible to determine the contributions of these components to the observed speech/language errors/arrest; we scored any such interference as ESM + as per usual clinical practice [11]. The

minimum current strength that elicited a reproducible speech/language error at an EC was defined as its threshold.

2.3. Language neuroanatomy for reference standard

We searched the National Institutes of Health funded Neurosynth database for "language" in the term-based mode, which extracted coordinates for language-related activation from 1101 published fMRI studies using an automated parser, and performed a meta-analysis by comparing the coordinates reported for studies with and without the term "language" [12]. From the voxelwise statistical inference maps output by Neurosynth, we extracted the language association test layer as 3D image dataset, which was used as the reference standard for functional neuroanatomy of language.

2.4. Image processing

Each patient had a presurgical MRI and a postsurgical computed tomographic (CT) scan of brain. The T1W sequence was coregistered to the fluid attenuation and inversion recovery (FLAIR) MRI using six parameter rigid body transformation. A tissue probability map was generated using this fused MRI data, to assign each voxel to gray matter, white matter, cerebrospinal fluid, bone, air, or other tissues. Using this tissue probability map, a nonlinear warping template was generated to transform images from individual patient space to the standard Montreal Neurological Institute (MNI) space. The CT was coregistered to the bone tissue from the MRI probability map and similarly transformed via the warping template into the MNI space. EC locations were then obtained from the transformed CT. Because all EC locations were now available in the MNI space, each EC was assigned to a brain parcel using the Medical Image Computing and Computer Assisted Intervention atlas [13]. The 3D language neuroanatomy obtained from Neurosynth meta-analytic fMRI framework was then intersected with EC locations to classify all ECs as lying within or outside the fMRI language parcels. The image processing was performed using SPM12 toolbox for MATLAB.

2.5. Outcomes and analysis

We compared the diagnostic validity of language ESM with meta-analytic fMRI functional neuroanatomy as the reference standard. We classified ECs as true positive if ESM + and lying within Neurosynth language parcel, false positive if ESM + but lying outside a Neurosynth language parcel, true negative if ESM − and lying outside Neurosynth language parcel, and false negative if ESM − but lying within a Neurosynth language parcel. Sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratio (DOR) were estimated along with their 95% confidence intervals (CI). An omnibus Mantel–Haenszel chi-square test was performed to test the primary hypothesis that DOR ≠ 1. Only stimulated ECs were included in the analyses.

We analyzed multivariable linear mixed models with language and AD thresholds as output variables, and age, age at onset of seizures, and full-scale intelligence quotient (FSIQ) as input variables. Since ECs are clustered under each patient, we regarded patient as the random effect in these mixed models. Statistical significance was obtained by comparing with a null model. We then compared language and AD thresholds for all ECs, for ECs lying in frontal and posterior cortical regions, and for those in gray and white matter, using t-tests for independent samples. We also compared language thresholds in ECs lying within (true positive) and outside (false positive) fMRI language parcels. Additionally, we compared AD thresholds in ECs with and without language response on ESM, and those lying within and outside fMRI language parcels. A nondirectional p ≤ 0.05 was regarded as significant. We also describe seizures triggered during ESM and the experience with low-frequency stimulation. Statistical analysis was performed with R version 3.5 [14].

Table 1
Cincinnati Children's Hospital protocol for electrical stimulation of stereo-EEG electrode contacts.

Setting	High frequency stimulation	Low frequency stimulation
Pulse frequency	50 Hz	1 Hz
Pulse duration	300 μs	≤500 μs
Train duration	5 s	≤30 s
Current strength	1–8 mA	1–8 mA
Suggested use	Functional mapping	Seizure induction

3. Results

Ten patients were included (5 females), aged 5.4–21.2 years (mean ± standard deviation 13.7 ± 5.2). Seizures began in these patients at 5 months to 15 years age (5.6 ± 4.3). Their FSIQ varied from 45 to 103 (73 ± 17). Functional magnetic resonance imaging was done in 8/10 patients and lateralized language to the left and right hemispheres in 6 and 2 patients, respectively. Functional magnetic resonance imaging could not be performed in 2 patients due to their inability to participate. Seven to 19 electrodes were implanted in these patients (11 ± 3), with 62–244 (114 ± 53) ECs. The number of ECs tested for language responses by ESM varied from 9 to 65 (31 ± 20). Other clinical details and reconstructions of electrode placements are provided in Table S1 and Fig. S1.

3.1. Diagnostic validity of language ESM with stereo-EEG

The spatial distributions of ECs where ESM produced and did not produce speech/language interference in relation to meta-analytic fMRI neuroanatomy (Neurosynth) are illustrated in Figs. 1 and 2, respectively. Stereo-EEG language ESM was a good classifier of fMRI (Neurosynth) language sites with a DOR of 9.02 (95% CI: 4.94, 16.57, p < 0.0001, Table 2). Electrical stimulation mapping showed high specificity 0.87 (0.83, 0.91), fair accuracy 0.76 (0.71, 0.81), but poor sensitivity 0.57 (0.50, 0.63), across all ECs. For 68/305 (22%) ECs in the frontal lobe, language ESM had a DOR of 13.98 (3.55, 59.44, p < 0.0001), with 0.88 (0.78, 0.95) specificity, 0.79 (0.67, 0.88) accuracy, and 0.65 (0.50, 0.76) sensitivity. For 237/305 (78%) ECs in posterior areas, language ESM had a DOR of 7.93 (4.01, 15.84, p < 0.0001), with 0.87 (0.83, 0.91) specificity, 0.76 (0.70, 0.81) accuracy, and 0.54 (0.46, 0.61) sensitivity. Similar patterns of diagnostic indices were seen with ECs lying either in gray matter (DOR: 8.19, 95% CI: 4.21–16.08, p < 0.0001) or white matter (DOR: 6.51, 95% CI: 1.12–39.08, p = 0.009).

3.2. Language and AD thresholds

Language and AD thresholds showed a significant decrease with age and FSIQ (Table 3, Fig. 3). Mean language threshold (3.1 ± 1.5 mA) was lower than mean AD threshold (4.0 ± 2.0 mA, p = 0.0001) for all ECs. In regional comparisons also, the language threshold was lower than AD threshold in frontal lobe (2.8 ± 1.3 vs. 4.8 ± 2.2 mA, p < 0.001) as well as posterior cortical regions (3.2 ± 1.5 vs. 3.8 ± 1.9 mA, p = 0.013). Language thresholds (3.2 ± 1.5 mA) were significantly lower than AD thresholds (4.2 ± 1.9 mA) in gray matter ECs (p = 0.0001) but not in white matter ECs (2.8 ± 1.1 vs. 3.5 ± 2.3 mA, p = 0.22).

Mean language thresholds were similar for ECs lying within (3.2 ± 1.5 mA) and outside (2.8 ± 1.4 mA) the fMRI language parcels (p = 0.254), for those lying in frontal (2.8 ± 1.3 mA) and posterior (3.2 ± 1.5 mA) cortical regions (p = 0.25), and for ECs lying in gray (3.2 ± 1.5 mA) and white (2.8 ± 1.1 mA) matter (p = 0.38).

After-discharges were seen in 9/10 patients, in 43 ± 24% of the stimulated ECs. Of the ECs with language responses, 55 ± 36% showed AD's. After-discharge threshold was lower in ECs with language responses (3.58 ± 1.5 mA) compared to those without language responses (4.2 ± 2.1), though this difference did not achieve statistical significance (p = 0.074). Also, mean AD threshold was lower in posterior (3.9 ± 1.9 mA) compared to frontal cortex (4.8 ± 2.2 mA), but these regional differences did not attain statistical significance (p = 0.081). After-discharge thresholds were similar in language ESM + ECs lying within (3.7 ± 1.5 mA) and outside (3.1 ± 1.7 mA) the fMRI language parcels (p = 0.382) and for all ECs lying in gray (4.2 ± 1.9 mA) and white (3.5 ± 2.3 mA) matter (p = 0.19).

3.3. Distribution of language responses

Language responses were noted on stimulation of 87/304 (29%) ECs. The most common response was nonspecific naming difficulty, including anomia and pauses/delay in naming (Table 4). In the left hemisphere, naming difficulty was most commonly noted on stimulations in superior temporal gyrus (STG, including adjacent transverse temporal gyri), and inferior frontal gyrus (IFG). However, naming difficulties were also occasionally noted on right hemisphere stimulation, most often in right STG. Isolated paraphasic errors localized only to the left hemisphere, most often to STG and pars triangularis of IFG. Pure dysarthria was rarely seen on stimulation of left STG and right supramarginal gyrus.
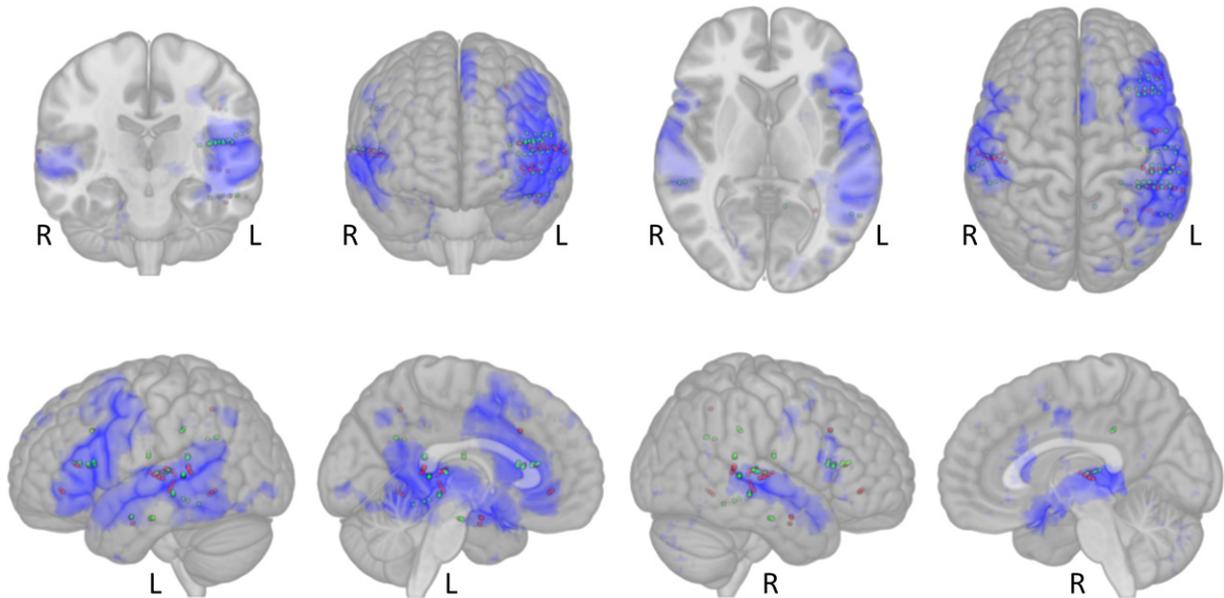
Fig. 1. Electrode contacts with language interference during electrical stimulation. Electrode contacts from all patients with language interference during electrical stimulation shown in Montreal Neurological Institute brain space in different sections. Language neuroanatomy obtained from meta-analysis of functional magnetic resonance imaging (fMRI) data from Neurosynth database is shown in blue. Electrode contacts lying within (true positive) and outside (false positive) the fMRI (Neurosynth) language parcels are shown in green and red, respectively. Since all electrodes have been projected on to the 2-dimentional figure, some of them may not represent their true locations in 3-dimensional space. The electrode contacts away from the plane of the figure have been blurred.
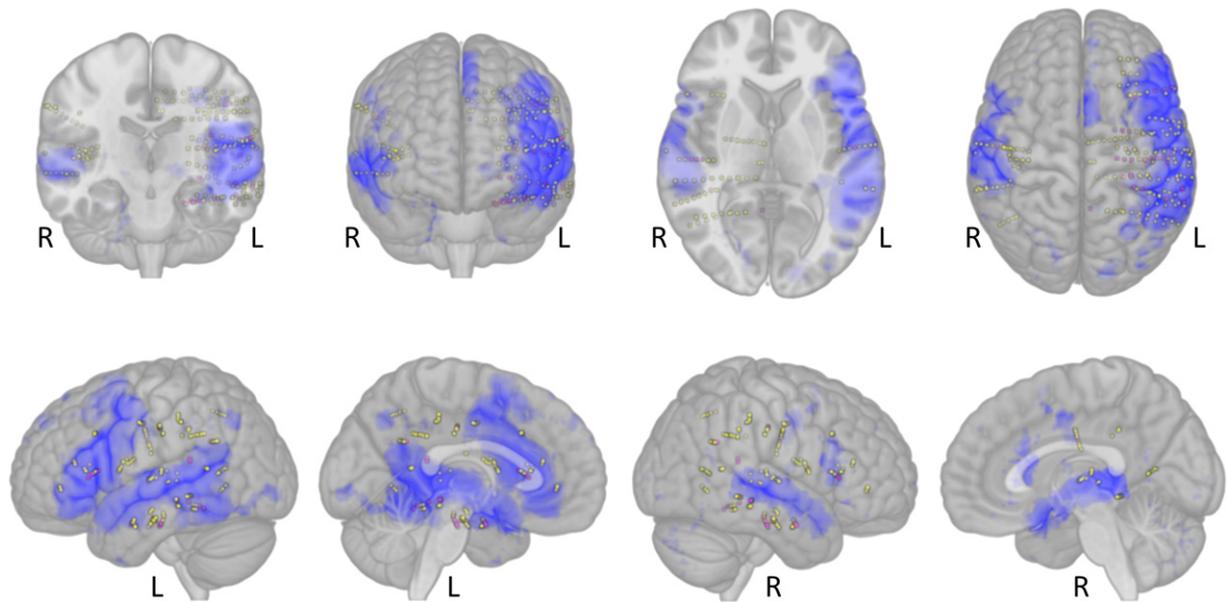
Fig. 2. Electrode contacts with no language interference during electrical stimulation. Electrode contacts from all patients without any language interference during electrical stimulation shown in Montreal Neurological Institute brain space in different sections. Language neuroanatomy obtained from meta-analysis of functional magnetic resonance imaging data from Neurosynth database is shown in blue. Electrode contacts lying within (false negative) and outside (true negative) the fMRI (Neurosynth) language parcels are shown in purple and yellow, respectively. Since all electrodes have been projected on to the 2-dimentional figure, some of them may not represent their true locations in 3-dimensional space. The electrode contacts away from the plane of the figure have been blurred.

3.4. ESM-triggered seizures

High-frequency stimulation triggered seizures in 3/10 patients, at 2 mA current in all three. In these 3 patients, the AD threshold was also 2 mA. Seizure semiology resembled habitual seizures in 2/3 patients.

3.5. Low-frequency stimulation

Low-frequency stimulation was performed in 6/10 patients. No reproducible language responses were produced. Habitual seizures were triggered in 2/6 patients while 2 other patients experienced aura resembling their typical seizure, which did not progress further.

4. Discussion

We found stereo-EEG language ESM to be a valid classifier of fMRI language parcels (Figs. 1, 2). Given the high specificity but fair sensitivity (Table 2), we think that ESM can dependably localize true negative sites but not all true positive sites. Because of the high positive likelihood ratio, if an EC is ESM+, it is likely to lie within language region. Considering both of these observations, we think that language ESM can reliably identify cerebral parcels without language function, but

may under detect those with language function. There are several possible reasons for this imperfect correspondence between stereo-EEG language ESM and meta-analytic fMRI neuroanatomy. Even with subdural electrodes, ESM language responses often occur discontinuously along an array [15,16]. Probabilistic cortical maps generated with intraoperative language mapping in a large (n = 250) study of patients with glioma, which are less susceptible to plastic reorganization compared to childhood-onset epilepsies, showed surprising variability in language localization within the dominant hemisphere [17]. Stereo-EEG further suffers from lack of contiguity over the cortical surface, though it allows access to deeper (mesial and basal) cortices. This sampling bias may contribute to under detection of language sites by stereo-EEG ESM. Our reference standard was derived from a meta-analysis of 1101 fMRI studies with heterogeneous samples including multiple ages, typically developing subjects as well as patients with epilepsy and behavioral disorders [12]. Since all voxels showing activation during any language task were included in the meta-analytic 3D neuroanatomy, it can potentially overrepresent the brain parcels participating in language processing. Comparatively, ESM is a transient lesion modality likely to identify only critical, and not all participating, language parcels [18]. In a study including 19 patients with drug-resistant epilepsy, the diagnostic validity of ESM–fMRI comparisons

Table 2
Diagnostic validity of electrical stimulation language mapping with stereo-EEG.

	All	Frontal	Posterior	Gray matter	White matter
Number of electrode contacts	304	68	237	231	73
Accuracy	0.76 (0.71, 0.81)*	0.79 (0.67, 0.88)*	0.76 (0.70, 0.81)*	0.74 (0.68, 0.79)*	0.84 (0.77, 0.91)*
Sensitivity	0.57 (0.50, 0.63)	0.65 (0.50, 0.76)	0.54 (0.46, 0.61)	0.59 (0.52, 0.65)*	0.36 (0.13, 0.61)
Specificity	0.87 (0.83, 0.91)*	0.88 (0.78, 0.95)*	0.87 (0.83, 0.91)*	0.85 (0.80, 0.90)*	0.92 (0.88, 0.96)*
Positive predictive value	0.71 (0.62, 0.79)*	0.77 (0.59, 0.90)*	0.69 (0.59, 0.78)*	0.74 (0.65, 0.82)*	0.44 (0.16, 0.74)
Negative predictive value	0.78 (0.75, 0.82)*	0.80 (0.72, 0.87)*	0.78 (0.74, 0.81)*	0.74 (0.69, 0.78)*	0.89 (0.85, 0.93)*
Likelihood ratio positive	4.46 (2.98, 6.75)*	5.49 (2.28, 14.84)*	4.18 (2.63, 6.73)*	3.94 (2.54, 6.23)*	4.51 (1.10, 16.03)*
Likelihood ratio negative	0.49 (0.41, 0.60)*	0.39 (0.25, 0.64)*	0.53 (0.43, 0.66)*	0.48 (0.39, 0.60)*	0.69 (0.41, 0.99)*
Diagnostic odds ratio	9.02 (4.94, 16.57)*	13.98 (3.55, 59.44)*	7.93 (4.01, 15.84)*	8.19 (4.21, 16.08)*	6.51 (1.12, 39.08)*
Mantel–Haenszel test	p < 0.0001	p < 0.0001	p < 0.0001	p < 0.0001	p = 0.009

* 95% confidence interval does not include point of no effect (0.5 for sensitivity, specificity, and predictive values; 1 for likelihood ratios and diagnostic odds ratio).

Table 3

Multivariable linear mixed models with language and after-discharge (AD) thresholds as functions of age, age at seizure onset, and full-scale intelligence quotient (FSIQ).

	Language threshold		AD threshold	
	Regression coefficient (95% CI)	p-Value	Regression coefficient (95% CI)	p-Value
Age	−0.21 (−0.07, −0.35)	0.002[*]	−0.15 (−0.03, −0.28)	0.010[*]
Age at onset	0.14 (0.32, −0.04)	0.066	0.08 (0.24, −0.08)	0.158
FSIQ	−0.04 (−0.01, −0.08)	0.012[*]	−0.06 (−0.02, −0.10)	0.001[*]

[*] p ≤ 0.05.

depended on the chosen radii of electrode regions-of-interest and statistical thresholding [19]. Similar to our observations, fMRI–ESM agreement was higher in patients with no ESM+ language sites [19]. We did not use individual patient fMRI as a reference standard for 2 reasons. First, while fMRI provides acceptable language lateralization in general, it has poor validity for patient-level localization sufficient enough to guide epilepsy surgical resections [20,21], which is the objective of ESM. Secondly, compared to our limited fMRI sample (8 patients), the meta-analysis (Neurosynth) offers a more generalizable reference standard for validating ESM.

We found a significant decrease in language and AD thresholds with age, similar to published experience with subdural electrodes [9,22]. The language thresholds declined more rapidly compared with AD thresholds (Fig. 3), suggesting that language and AD thresholds may be similar in younger children. However, mean language thresholds were below mean AD thresholds, for overall and regional comparisons. This is contrary to the observations from subdural electrodes [9,22,23]. In a study including 122 patients aged 0.9–26 years, AD threshold was lower than language threshold throughout the age range [9]. Our finding is difficult to explain, because our understanding of the geometry of current propagation after stimulation of subdural or stereo electrodes, and its interaction with pyramidal cells and interneurons for response generation, is severely limited [24,25]. Animal studies have shown that orientation of cell bodies and axons with respect to current flow determines the chronaxies (and in turn, rheobase current strengths) for electrical stimulation of central myelinated fibers [24]. This is relevant because the orientation of the subdural electrodes is perpendicular, whereas that of the stereo electrodes is relatively parallel to the long axis of pyramidal cells, at least in cerebral convexity, because our stereo electrodes were implanted orthogonal to the cerebral surface. An interesting observation was that language threshold was below AD threshold in gray but not white matter. We speculate that ESM with stereo ECs results in functional interference in a smaller volume brain tissue, whereas stimulation of a pair of subdural electrodes leads to current spread through local white matter in addition to cortex, thereby obviating this threshold differential. This is consistent with significantly higher impedance in white matter compared to gray matter noted in a study with simulation of current flows in the local brain volume after intraoperative focal current injections in 15 patients with epilepsy [26].

Language and AD thresholds also showed a significant decline with increasing FSIQ (Table 3), suggesting that patients with higher FSIQ have more excitable brains. This is consistent with our recent observation that baseline FSIQ is an important determinant of information sharing in the perisylvian language networks [27]. Event-related potential experiments with auditory oddball task have also shown more efficient engagement of neuronal networks with higher FSIQ [28]. Additionally, language thresholds were higher than AD thresholds in children with FSIQ>81 (Fig. 3), suggesting that patients with higher IQ may be more susceptible to ESM-triggered seizures. The influence of intelligence on physiologic and pathologic cortical excitability, characterized by functional and AD thresholds respectively, could be an attractive avenue for future studies.

After-discharges were seen in 90% of patients (in 43 ± 24% of the stimulated ECs), compared with 48%–90% incidence in previous studies of subdural electrodes [29–32]. Seizures were triggered with high-frequency stimulation in 3/10 (30%) patients, at a current identical to AD threshold. This agrees with a prior study including 122 patients with subdural electrodes which noted ESM-triggered seizures in 35% patients, showed that ADs were associated with higher odds of ESM-triggered seizures, and that AD and seizure thresholds were comparable [29]. In 1/3 of our patients, the semiology of ESM-triggered seizure was different from the patient's habitual seizures. While low-frequency stimulation failed to produce any consistent language responses, it did trigger seizures in 2/6 (33%) patients and aura in another 2 patients. These seizures were similar to the patients' typical seizures, and the aura in both the cases resembled the habitual aura at the onset of patients' seizures. A possible explanation for this observation may be that ECs where 50 Hz stimulation triggered seizures, were distant from spontaneous SOZ (the same lobe in 2 patients, different lobe in 1 patient), while ECs where 1 Hz stimulation produced seizures/aura overlapped with spontaneous SOZ, and helped clarify the causal significance of SOZ [33]. This also led us to speculate a tendency for high-frequency stimulations to propagate, such that the functional effects may not be strictly localized to stimulated brain tissue.

These findings have important implications for epilepsy surgery and challenge some of the prevailing viewpoints such that language cannot be adequately mapped with stereo-EEG and it is better to implant subdural grids if SOZ is close to language cortex; base surgical strategy on canonical anatomy; or the suggestion to use low-frequency stimulation for functional mapping with stereo-EEG [6,34]. Because language ESM was found to have high specificity and high negative predictive value, it can sufficiently define the cortex safe for resection. However, although language ESM can classify "some" language sites correctly (high positive predictive value and DOR), it is unlikely to detect "all" language sites (poor sensitivity with 95% limits including point of no effect except for gray matter comparison, Table 2). Hence, we suggest that high-frequency ESM should be first performed for language mapping with stereo-EEG, and subdural grids can be considered as a second stage only in cases where there is a concern for false negative ESM sites within the SOZ. In clinical practice, this decision should also incorporate results of noninvasive language lateralization. It has also been suggested that the primary use of electrical stimulation of stereo ECs is to reproduce patient's typical seizures, and any transient speech/language deficit during such stimulation should be interpreted only in the context of seizure semiology [6]. Since our study was agnostic to the location of SOZ by design, we posit that stereo-EEG language ESM can be used by itself. We also believe that language ESM with stereo-EEG may be safer than with subdural grids, given that language thresholds were below AD thresholds for stereo-EEG. Based on our findings, we suggest using high-frequency stimulation for language mapping and low-frequency stimulation to attempt reproduce habitual seizures when required (Table 1).

Our study presents a prospective validation of language ESM with stereo-EEG. Nevertheless, it has some unavoidable limitations, including a modest sample size. We used a 3D dataset obtained from meta-analysis of 1101 fMRI language studies as our reference standard, raising concerns about sample heterogeneity, and mechanistic discrepancy between perfusion changes detected by fMRI and functional interference produced by ESM. Perhaps, the best gold standard will be the postoperative language deficits assessed by neuropsychological evaluation, which represent the true functional impact of neurosurgery. However, because surgical resections incorporate ESM results, there is an inherent bias. Since the steady-state neuropsychological deficits are typically evaluated ≥1 year after surgery, and our stereo-EEG program started only in late 2016, we hope to assess the relationship between language ESM, anatomy of surgical resection, and long-term neuropsychological outcomes in future [35]. Also, it is our practice to use a visual naming task for ESM. However, ESM in subdural electrodes has shown task-
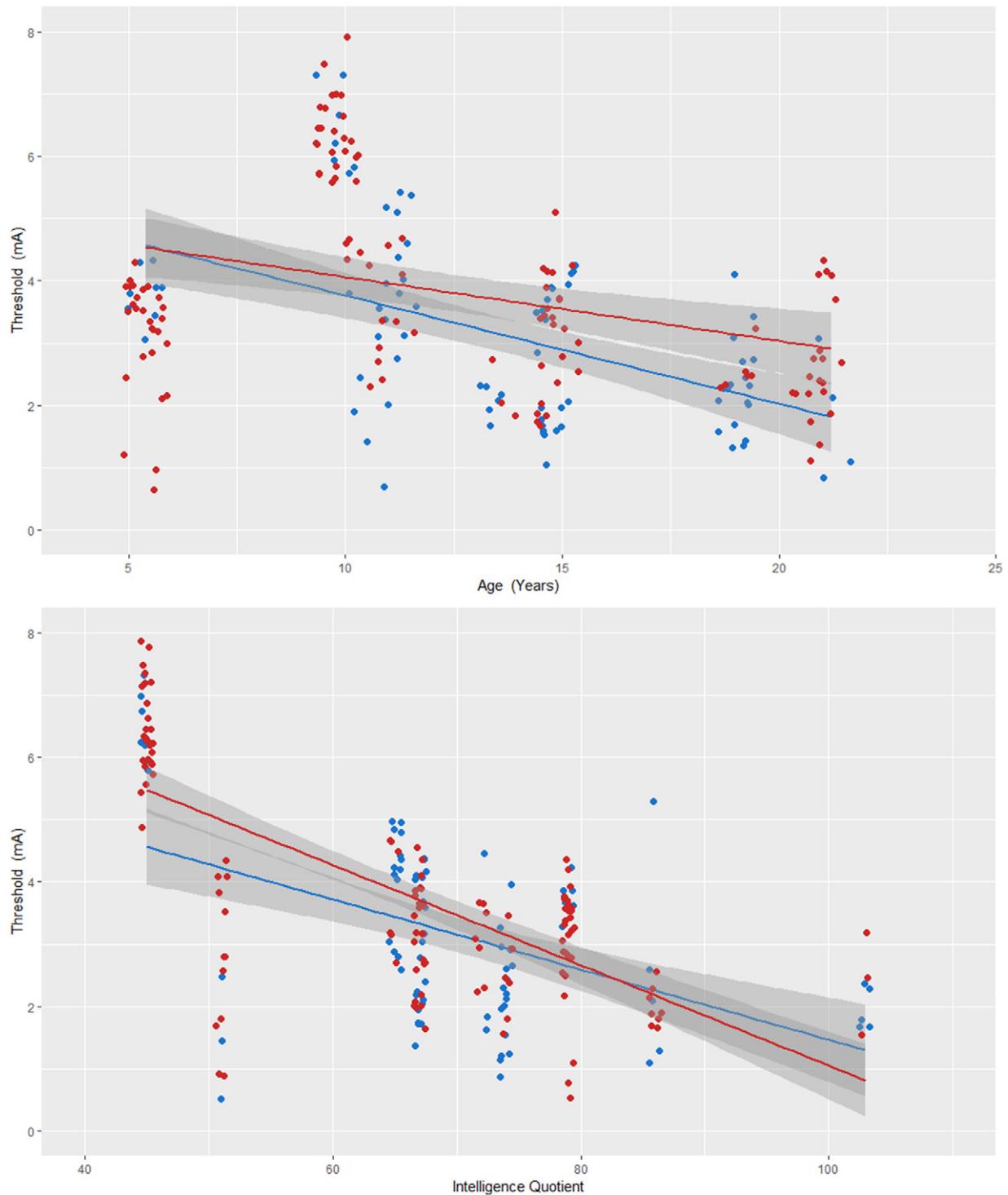
Fig. 3. Language and after-discharge thresholds as functions of age and intelligence quotient. Language (blue) and after-discharge (red) thresholds as functions of age (upper panel) and full-scale intelligence quotient (lower panel). Although data were analyzed using mixed models, ordinary least-squares regression lines are shown with 95% confidence envelopes, for the ease of display.

specific patterns for language responses [11]. In particular, both ESM and event-related power modulations in electrocorticographic spectra have shown similarities and differences in the localization of responses to picture and auditory naming tasks. In posterior language regions, responses to picture and auditory naming have typically localized respectively medial and lateral to inferior temporal gyrus; and while anterior language regions including Broca's area have shown activation with both tasks, activation with picture naming is typically earlier than that with auditory naming, on a time-resolved analysis [36,37]. Hence, it

remains open to investigate the clinical utility of different tasks for language ESM with stereo-EEG, particularly in relation to age or FSIQ of different patients. Although at present, ESM with subdural electrodes is the clinical gold standard for language localization with intracranial EEG, we expect language ESM with stereo-EEG to have similar validity based on our observations and improving neurosurgical capability for higher density stereo-EEG. Also, the limitations of ESM with subdural grids have prompted development of alternate methodology for language mapping with task-related high-gamma power modulations

Table 4
Topographic distribution of language responses in the left and right hemispheres.

Language response	Left cerebral hemisphere	N,%	Right cerebral hemisphere	N,%
Naming difficulty (n = 77)	STG, Heschl's gyrus, and planum temporale	18, (23.4%)	STG, Heschl's gyrus, and planum temporale	4, (5.2%)
	IFG pars triangularis	9, (11.7%)	White matter (temporal)	2, (2.6%)
	IFG pars opercularis	9, (11.7%)	Postcentral gyrus	1, (1.3%)
	White matter (frontal)	8, (10.4%)	Angular gyrus	1, (1.3%)
	Middle temporal gyrus	5, (6.5%)		
	Angular and supra-marginal gyri	4, (5.2%)		
	Postcentral gyrus	4, (5.2%)		
	Amygdala	3, (3.9%)		
	Parahippocampal gyrus	3, (3.9%)		
	Hippocampus	2, (2.6%)		
	White matter (temporal)	1, (1.3%)		
	Inferior temporal gyrus	1, (1.3%)		
	White matter (parietal)	1, (1.3%)		
	Fusiform gyrus	1, (1.3%)		
Paraphasic errors (n = 25)	STG, Heschl's gyrus, and planum temporale	9, (36.0%)		
	IFG pars triangularis	5, (20.0%)		
	Postcentral gyrus	3, (12.0%)		
	Supra-marginal gyrus	3, (12.0%)		
	White matter (frontal)	2, (8.0%)		
	Hippocampus	2, (8.0%)		
	IFG pars opercularis	1, (4.0%)		
Dysarthria (n = 7)	STG, Heschl's gyrus, and planum temporale	3, (42.9%)	Supra-marginal gyrus	2, (28.6%)
	Middle frontal gyrus	1, (14.3%)	White matter (temporal)	1, (14.3%)

Note: Language responses were seen on stimulation of 87 electrode contacts. However, some contacts showed >1 type of language response (on repeat stimulation or stimulation at higher current), hence, the total is more than 87. IFG: inferior frontal gyrus; STG: superior temporal gyrus.

that allow studying connectivity and spatiotemporal dynamics of language networks instead of the binary classification of brain sites obtained from ESM [27,36,38,39]. In future, we hope that the methodology of high-gamma modulation language mapping can be extended to stereo-EEG, where it will probably supplement ESM, and improve safety and access of epilepsy surgery.

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