Source Localization of Tripolar Electroencephalography

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SOURCE LOCALIZATION OF TRIPOLAR ELECTROENCEPHALOGRAPHY

BY

CHRISTOPHER TOOLE

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN NEUROSCIENCE

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OF
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ABSTRACT

Knowing where sources of electroencephalography (EEG) signals are located in the brain can help with diagnosis and surgical planning for patients with epilepsy. Source localization of signals acquired on the scalp is an ill-posed problem since there are an infinite number of inverse configurations that can result in the same potential distribution on the head surface. Therefore, additional constraints to the source space must be used to find a unique solution. Distributed source methods constrain the source space to a large number of dipoles distributed on the cortical surface or within the brain, but they yield an underdetermined solution. Used with conventional EEG and its limited spatial resolution, these localization methods produce poor resolution. There exists a need to better localize sources of activity measured on the scalp before the use of invasive procedures and their risks. Tripolar EEG (tEEG), i.e., EEG recorded with the tripolar concentric ring electrode (TCRE), has increased spatial resolution and signal-to-noise ratio, and it more readily detects high frequency biomarkers of epileptogenic zones than conventional, noninvasive measurements. This research explores the effects of these tEEG advantages on localization with distributed source methods and its potential in clinical use.
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I also dedicate this thesis to my mother Paulette, the rock of our family, and my brothers Mike and Neil, my two best friends. I wouldn’t be where I am without you guys.

And Lauren, your unwavering support and dedication through trying times make all this possible. I can’t express my appreciation enough. Your love means everything to me, and the life we have started to build is more than I could ever ask for. You and our pups, Stella and Dex, make everyday enjoyable. I love you and dedicate this thesis to you and our pack.
The first human electroencephalogram (EEG) was recorded in 1924 by German physiologist and psychiatrist Hans Berger. Lacking a technical background and formal training in mechanics and electricity, Berger invented the first EEG device. It took the work of British electrophysiologists Edgar Douglas Adrian and B.H.C. Mathews to validate Berger’s discoveries in electroencephalography (EEG) in 1934, and by 1938, EEG methods were widely accepted and used for clinical diagnosis in the United States, England, and France.

By measuring potential differences on the scalp surface, EEG is used to monitor the ionic currents in the brain produced by neuronal signaling. Post-synaptic extracellular currents that follow neurotransmitter transmission are the main contributors to scalp EEG. When networks of neurons of similar spatial orientation synchronously fire action potentials, the resulting extracellular currents produce an electric field sufficient for detection on the scalp. Thus, EEG is helpful in the diagnosis of conditions that cause abnormal signaling in the brain such as epilepsy.

Even after the invention of numerous neuroimaging techniques, EEG is still used today for diagnosis. It’s cost, temporal resolution, minimal risk, and ease of use make EEG an invaluable tool. It suffers from poor spatial resolution, low signal-to-noise ratio, and struggles to detect activity from deep brain structures, but other brain measurement methods developed to alleviate these drawbacks are either costly, have poor temporal resolution, or are invasive which introduce risks to subjects. Processing techniques such as Laplacian spatial filtering aim to increase the spatial resolution of EEG. In a Laplacian montage, each channel represents the difference between an electrode and a weighted average of the surrounding electrodes, amplifying high spatial frequency components and electrical activity generated close to the channel location. However, spatial resolution increase with
Laplacian filtering is limited by electrode size, spacing, and number of channels.

Laplacian filtering served as the basis for the development of the tripolar concentric ring electrode (TCRE) by Dr. Walter Besio in 2006. The electrode consists of three concentric, conductive rings in a bullseye configuration. Each ring acts as its own EEG electrode, and a focal Laplacian can be approximated by taking a weighted sum of two bipolar measurements between the rings. EEG recorded with the TCRE, tripolar EEG (tEEG), shows greater signal-to-noise ratio and spatial resolution when compared to conventional EEG. The present body of work explores the use of dipole modeling source localization with tEEG signals. These methods employ head models with dipoles distributed over the cortex. Dipole activations and the resulting scalp potentials are fit to recorded data to estimate source regions. The thesis is written in manuscript style format and contains two manuscripts. The first manuscript has been submitted to Brain for publication and focuses on the localization of high frequency epilepsy biomarkers. These high frequency signals are more difficult to detect in conventional EEG than tEEG, and their sources are indicative of seizure generating tissue. The second manuscript is being prepared for submission and is meant to elucidate the effect of increased spatial resolution and signal-to-noise ratio in tEEG on the resulting source maps of distributed source dipole modeling.

In addition to these two manuscripts, the appendix contains three sections. Appendix A provides additional background information for both manuscripts, and Appendix B contains discussion on the results of both papers, implications of the presented body of work, and future directives of source modeling of tEEG signals. Appendix C contains the results of a single subject after altering the recording methods of manuscript 2 and supports the discussion found in Appendix B.
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Source Localization of High Frequency Activity in Tripolar Electroencephalography of Epilepsy Patients

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Manuscript is currently under review for publication in Brain.
1.1 Abstract

High frequency oscillations (HFOs) have been studied as precise biomarkers of the seizure onset zone (SOZ) in epilepsy, and these regions are removed to good therapeutic effect in surgical candidates. Knowing where the sources of these highly focal events are located in the brain can help with diagnosis. HFOs are not commonly observed in noninvasive electroencephalogram (EEG) recordings, and invasive electrocorticography (ECoG) is usually required to detect them. However, tripolar electroencephalography (tEEG), i.e., EEG recorded on the scalp with tripolar concentric ring electrodes (TCRE), has been found to detect narrowband, high frequency activity (HFA) that correlates with SOZ diagnosis. In the present study, performed on nine patients with epilepsy, HFA observed in the tEEG were localized to the surface of subject-specific, realistic, cortical models, and found to occur almost exclusively in the SOZ/IZ (irritative zone). Thus, source localization of HFA in tEEG may help clinicians identify brain regions for resective epilepsy surgery. At the least, the tEEG HFA localization may help determine where to perform intracranial recordings used for precise diagnosis.

1.2 Introduction

Epilepsy affects approximately 70 million people worldwide, making it the second most prevalent neurological disorder [1]. Of all epilepsy patients, 60% suffer focal epilepsy syndromes and approximately 15% of these patients suffer conditions resistant to anticonvulsive drugs. Rosenow and Luders [2] conservatively estimate that approximately 50% of these patients are potential candidates for surgical epilepsy treatment, 4.5% of all epilepsy patients. In surgery, seizure onset zones (SOZs) or irritative zones (IZs) are removed with good therapeutic effect [3]. The SOZ is defined as the region in which clinical seizures originate, while the IZ is the region of cortex that generates inter-ictal epileptiform discharges seen in EEG or
magnetoencephalography (MEG) measurements [2]. Thus, EEG potentials play an important role in evaluating suitability for epilepsy surgery [4]. SOZs and IZs must be correctly identified and localized before surgery [3]. However, conventional EEG has poor sensitivity to localized epileptiform activity such as HFOs [2].

HFOs can refer to abnormal gamma activity (30-100 Hz), ripples (100-200 Hz), or fast ripples (250-500 Hz) and were first reported in humans by Fisher et al. [5] and Allen et al. [6]. They are high energy oscillations which have been shown to be a biomarker of epilepsy and highly correlated with the SOZ and IZ [7, 8, 9]. Because HFOs arise from synchronous firing of small, focal subsets of neurons, intracranial recordings are typically required to detect their localized presentation [10]. HFOs have been recorded in the minutes before seizure onset, and the removal of their cortical sources, especially for fast ripples, correlates with positive surgical outcome [5, 6, 7, 8, 11, 12, 13, 14, 15, 16]. The sources of fast ripple activity in humans are estimated to be less than 1 mm$^3$ [17]. Thus, microwire electrodes are best suited for their detection. However, Worrell et al. (2008) have recently shown that detection of HFOs in this frequency range is possible with clinical macroelectrodes on the scale of 1 to 10 mm$^2$. They utilized hybrid depth electrodes containing both clinical electrocorticography (ECoG) sensors and multiple microwires and found that HFO frequencies recorded with microwires span a continuum from the ripple to the fast ripple range. In contrast, the distribution of HFO frequencies recorded with macroelectrodes falls off more rapidly with frequency, and fast ripples are observed less frequently [15].

Each sensor in conventional, scalp EEG represents a spatial average of active current sources distributed over a large, macroscopic volume of brain space [18], which contributes to the spatial aliasing of cortical sources. Moreover, the spatial filtering properties of the skull and soft tissues between cortex and scalp have a
blurring effect on closely spaced sources due to volume conduction. High frequency sources are small, tightly packed neuron populations, whereas lower frequencies tend to have more distributed sources. Thus, the spatial filtering has the appearance of a low pass filtering characteristic, despite the fact that the impedance between the cortex and scalp is similar for low and high EEG frequencies [19]. This effect makes the skull, with the adjoining soft tissue, a major obstacle to noninvasive HFO detection and localization.

Besio et al. [9] have shown that the tripolar concentric ring electrode (TCRE) (Figure 1.1) is able to noninvasively record narrowband, high frequency activity (HFA) in epilepsy patients. The term HFA is used to differentiate this apparent epileptic activity from previously reported, more wideband HFOs. The increased signal-to-noise ratio and spatial resolution of the TCRE [20, 21, 22, 23] make noninvasive measurement of HFA possible in tEEG. The novelty of the TCRE design and instrumentation is that two bipolar signals are recorded from three closely spaced, concentric electrode elements. Then the tripolar Laplacian derivation, first described in Besio et al. [20], is estimated as the weighted sum, \(16^*(M-D)-(O-D)\), where O, M, and D are the potentials on the outer ring, middle ring, and central disc of the TCRE, respectively. When compared with conventional EEG signals, tEEG has shown a 6.25 dB increase in signal to noise ratio and less than one-tenth (8.27%) the mutual information between a pair of adjacent electrodes [20, 23]. Localization of HFA sources by approximation to the nearest electrode(s) [9] has been performed, but more robust methods such as discrete dipole fitting or distributed source methods have yet to be reported with any tEEG signals.

This study seeks to localize HFA in epilepsy patients to realistic, subject-specific cortical models in the hope that HFA sources are highly correlated with SOZ/IZ clinical diagnosis and could be used as a preliminary indicator of these
epileptogenic zones. Consequent identification of SOZs and IZs through tEEG source localization would increase confidence in determining areas for removal in epilepsy surgery. Since these procedures, including invasive EEG (iEEG), are associated with risks to patients including transient and permanent neurologic deficits, infections, hematoma, non-habitual seizures, cerebral infarction, cerebral edema, and increased intracranial pressure [24, 25], it is advantageous to have a better understanding of individual pathology before patients are subject to them.

1.3 Methodology
1.3.1 Subjects

Patients were recruited from Rhode Island Hospital (RIH; n=1) and the National Institute of Neurology and Neuroscience (NINN; n=8) in Mexico City, Mexico after referral by the epilepsy clinic of each institution with the diagnosis of drug-resistant epilepsy, using the International League Against Epilepsy criteria [26]. Epilepsy and epileptic seizure diagnosis was based on the international classification of seizures 1981 [27] and epileptic syndromes 1989 [28]. Recording protocols were approved by each of the institutional review boards. SOZ diagnosis was performed by an epileptologist at NINN (IEMJ) and RIH (JNG).
1.3.2 Data collection

The tEEG recording protocol was designed to avoid any interference with clinical EEG recording and evaluation. At both the NINN and RIH during the attachment of clinical conventional disc electrodes (referred to as 'EEG electrodes' or 'EEG signals' in the subsequent text), the patient’s scalp was cleaned with Nuprep and then EEG electrodes were affixed to the scalp at the 10-20 International Electrode System locations using Ten-20 paste (and collodion at NINN). To obtain tEEG recordings in parallel to the clinical EEG, the TCREs were placed just behind the disc electrodes in 19 locations close to the 10-10 sites and attached to the scalp with Ten-20 paste (and collodion at NINN) (Figure 1.2). The electrical ground was placed on the forehead, and the reference electrode was placed on the forehead at RIH and on the Oz location at NINN. Clinical EEG was recorded with the Comet AS40 system (Grass Technologies, West Warwick, RI) and stored separately for further clinical evaluation. The clinical EEG was digitized at 200 samples per second and the low-pass filter was 70 Hz. The tEEG data were pre-amplified with the gain equal to either 6 (n=5) or 47 (n=4) and amplified and digitized with an Aura LTM-64 system (Grass Technologies, West Warwick, RI) at different sampling frequencies for different patients. For two patients the data were filtered from 1-100 Hz and digitized at 200 S/s, another one was filtered from 1-200 Hz and digitized at 400 S/s and for the remaining six patients the data were filtered from 1-500 Hz and digitized at 1600 S/s. The 60 Hz notch filter was used for all patients. The recording sessions at the NINN usually lasted for six hours, from around 7am to 1pm. For the patient at RIH, the recording was stopped shortly after the patient had a seizure (130 minutes total). The NINN recording protocol included requests that patients be sleep deprived the night before coming in for video-EEG monitoring and all patients signed an additional consent form.
as antiepileptic drugs dosage was reduced by half the day before the recording. Recorded data were reviewed by the epileptologists, and seizure onset time and duration were determined for each seizure. Seizure onset time was defined as the beginning of the first observable seizure pattern in EEG.

Figure 1.2. The 10-5 montage with TCREs (red) placed near the 10-20 locations. Note: T7/P7 and T8/P8 are the same as T3/T5 and T4/T6 in 10-20 nomenclature. The blue rings are for standard 10-20 electrode locations.

1.3.3 Head modeling

T1 weighted MR images of 7 NINN patients were available for 3-dimensional, subject-specific, realistic head modeling. Head models were constructed from these images with the automated procedures of the Freesurfer image analysis suite. Freesurfer is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Prior publications (Dale et al. [29]; Fischl and Dale [30]; Fischl et al. [31, 32, 33, 34, 35, 36]; Han et al. [37]; Jovicich et
al. [38]; Segonne et al. [39], Reuter et al [40, 41]) describe the technical details of the Freesurfer procedures. In the present study, only a single series of volumetric T1 images was used for each subject. Therefore, motion correction and averaging was not performed. In the Freesurfer process, a hybrid watershed/surface deformation procedure [39] is used to remove non-brain tissue and is followed by an automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures [32, 33], intensity normalization [42], tessellation of the gray matter white matter boundary, automated topology correction[31, 43], and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [29, 30]. Subject models were exported from Freesurfer and imported into Brainstorm for localization analysis. Brainstorm calls OpenMEEG [44] to convert the Freesurfer output into a three layer boundary element method (BEM) model surrounding the source space of 15,000 dipoles on the cortex surface. These layers include the scalp, skull, and brain with relative conductivity values of 1, 0.0125, and 1, respectively, and each layer consists of 1922 vertices. OpenMEEG then used the BEM to calculate the lead field matrix. Conversion to a tEEG specific lead field matrix was not performed, as forward model resolution was not sufficient for obtaining differences in potential on the model surface between TCRE rings.

1.3.4 Signal Processing and Localization

The data from individual TCRE rings was first preprocessed with the tripolar Laplacian algorithm [22] to obtain the tEEG signal for each electrode. This signal estimates the surface Laplacian by multiplying the difference between the inner ring and center disc by a factor of 16 and then subtracting the outer ring signal. As in Besio 2014 [9], a modified version of the algorithm reported by Gardner et
al. [45] was used in Matlab for detection of HFAs and their frequency characteristics. High frequency artifacts were ruled out for localization by visual inspection. Spectrograms were used to identify persistent, narrowband HFA in the pre-ictal recordings.

Data was imported into EEGLab (https://sccn.ucsd.edu/eeglab/), a freely available plugin for MATLAB. EEG and tEEG recordings were de-trended and notch-filtered (non-causal, zero-phase, IIR Butterworth) to remove DC bias and 60 Hz noise respectively. Then a non-causal, zero-phase, IIR Butterworth band-pass filter specific to each subject’s HFA range was used to isolate the narrow-band, high-power activity of each subject. Filters were designed to avoid both loss of gain in the passband and the introduction of ripple artifacts. Data was then imported into Brainstorm [46], which is a freely available (http://neuroimage.usc.edu/brainstorm/) open-source application for the analysis of MEG, EEG, fNIRS, ECoG, and other brain recordings.

In Brainstorm, surface potentials of the HFA peaks were localized, on a case-by-case basis, to the surface of cortical models specific to each subject, where available, and the ICBM152 head model was used for patients with no MRI data. The ICBM152 model is derived from a non-linear average of MRI scans of the 152 subjects in the MNI152 database [47, 48]. Only persistent HFA were selected for localization. If multiple locations recorded this activity, then each was used for localization. A whitened and depth-weighted linear L2-minimum norm estimates (MNE) algorithm [49] was used to localize signals to a source space of dipoles constrained normal to the cortical surface of the model, resulting in current density plotted on the model cortical surface. For a full description of this localization method, please refer to section 6, ”The current estimates”, of the MNE manual [50], which is available for download (http://www.martinos.org/meg/manuals/
1.3.5 HFA localization and correlation with SOZ/IZ Diagnosis

To assess the relationship between the identified HFA sources and the clinical diagnosis, the ratio of patients in which HFA generators fell within the SOZ/IZ over the total number of patients was calculated. The ratio of patients in which HFA was localized to areas outside the SOZ/IZ was also calculated to assess the selectivity of HFA as an indicator of SOZ/IZ. The SOZ or IZ was determined for each patient by the epileptologists based on EEG data, video EEG, patient history, and medical imaging such as MRI and PET. These clinicians did not have access to tEEG data and were not aware of the HFA detection and localization results. In one patient, the SOZ was determined by intracranial ictal recordings and seizure cessation following surgical resection.

1.4 Results
1.4.1 HFA detection and Localization

Epileptiform HFA was found and localized in the tEEG recordings of nine epilepsy patients. Eight of these subjects experienced clinical seizures during recording, and T1-weighted MRI data was available for the construction of seven subject-specific head models. The ICBM152 average head model was used for the remaining two subjects. Localized HFA fell into the high gamma, ripples, and fast ripples range in three subjects each. These findings are summarized in Table 1.1, which shows the source location of HFA, the frequency of this activity, SOZ/IZ diagnosis, whether or not the source location and diagnosis agree, if additional sources were found outside the diagnosed SOZ/IZ, and the head model (ssm = subject-specific head model) for each subject.
### Table 1.1. Summary of HFA localization results

| Patient | HFA source                                      | Frequency (Hz) | SOZ/IZ                        | Agree? | Outside? | Head model |
|---------|-----------------------------------------------|----------------|-------------------------------|--------|----------|------------|
| A       | Left frontotemporal                           | 120            | Left frontotemporal            | Yes    | No       | ssm        |
| B       | Left occipital                                | 75             | Left occipital/parietal        | Yes    | No       | ssm        |
| C       | Bilateral frontotemporal                      | 75             | Bilateral frontotemporal       | Yes    | No       | ssm        |
| D       | Nonfocal                                      | 330            | Nonfocal                      | Yes    | N/A      | ssm        |
| E       | Right motor/frontal, left motor/temp./front./par | 63             | Left premotor                 | Yes    | Yes      | ICBM152    |
| F       | Right temporal                                | 394            | Bilateral temporal            | Yes    | No       | ICBM152    |
| G       | Right frontotemporal, left temporal/parietal | 320            | Right frontotemporal          | Yes    | Yes      | ssm        |
| H       | Right temporal                                | 110            | Right temporal                | Yes    | No       | ssm        |
| I       | Left temporal/parietal/occipital              | 110            | Left parietotemporal          | Yes    | Yes      | ssm        |
Figure 1.3. A representative example of the HFA recorded in patient G shown in the time domain (a) and its power spectral density (b). Activity below 55 Hz and above 500 Hz was filtered, forward and backward for zero phase, with a fifth order Butterworth IIR filter. HFA is most prominent at approximately 238.5 seconds in TCRE channels P3, O1, Pz, and F8. The four largest peaks at 320 Hz in (b) are of the same four channels.

A representative example of the recorded HFA in patient G is shown in Fig-
Figure 1.4. Spectrograms of the HFA signals (circled) shown in Figure 1.3, built from short time Fourier Transform with 1 second Hamming windows of 50% overlap. TCRE channels P3 (A), O1 (B), Pz (C), and F8 (D) are shown. Circled activity is localized in Figure 1.5. Activity below 55 Hz and above 500 Hz was filtered, forward and backward for zero phase, with a fifth order Butterworth IIR filter. A 60 Hz notch filter was also applied.
Figure 1.5. Source localization results of HFA peaks recorded in the tEEG of patient G at approximately 238 s into recording segment. Approximately 8 minutes prior to a complex partial seizure. Approximate seizure onset zone is circled in red.
ure 1.3. At the time of recording this patient was a 62-year-old male with a right frontotemporal lobe SOZ diagnosis. He had been experiencing complex partial seizures (CPS) with a frequency of one per month and was being treated with 500mg Levetiracetam (LEV). MRI had revealed a left temporal encephaloma and issues with the intensity of the white subcortical and deep matter in the left temporal lobe. The same region exhibited hypometabolism in PET imaging. Figure 1.3(a) displays the tEEG time series of a 1-second segment containing a HFA at the 238.5 second mark, preceding a complex partial seizure by approximately 8 minutes. HFA is apparent at locations P3, O1, Pz, and F8. The power spectral density of the same segment of data can be found in Figure 1.3(b). A sharp peak is visible at 320 Hz for those four channels but not the others.

Figure 1.4 shows the spectrograms for channels P3, O1, Pz, and F8 in panels (a), (b), (c), and (d), respectively. Persistent 320 Hz activity is seen in all four channels. The exact instant shown in Figure 1.3 can be seen at approximately the 238 second mark, soon after the first instance of increased power across all frequencies. Peaks of this HFA example were then localized on the cortex surface of the subject-specific model and shown in Figure 1.5. Figure 1.5a contains the localization of moderate HFA generated outside of the SOZ, while 1.5(b)-1.5(d) display stronger HFA localization within the SOZ.

### 1.4.2 SOZ/IZ Correlation

HFAs preceding seizures were localized to the SOZ in eight of the nine patients. No SOZ was determined in the remaining patient, so HFA source map correlation to the IZ was accessed instead. The seizure of this patient (D) was determined to be of non-focal onset and widespread HFA sources were observed, so patient D was excluded from accessing the selectivity of HFA sources as indicators of SOZ. The HFA sources of patient D were considered within the SOZ/IZ for correlation.
calculation. HFA were localized within the diagnosed SOZ/IZ in all nine of the patients (100%). A focal diagnosis was determined for eight patients. In only three of these patients (37.5%), sources of HFA above noise levels were found outside of the SOZ/IZ. Figure 1.5(a) is an example of HFA sources found outside the diagnosed SOZ (Right frontotemporal region circled in 1.5(b)-1.5(d)) of Patient G.

1.5 Discussion

EEG source localization (ESL) is fundamentally broken into the forward and inverse problem when determining cortical sources of signals measured on the scalp surface [51, 49]. Identification of the source from signal is the inverse problem. The forward problem is the propagation of signals from source to the scalp surface, and its solution, the forward model, is necessary to solve the inverse problem [52]. Specifically, the head model, and its compartments, surfaces, conductivities, and co-registered electrode locations comprise the forward model, also known as the volume conductor [51].

The inverse problem is ill-posed since there are an infinite number of source configurations that can result in the same potential distribution on the head surface. Therefore, additional constraints to the source space must be used to find a unique solution. Distributed source methods constrain the source space to many dipoles distributed either on the cortical surface or within the brain, but they yield an underdetermined solution. These methods allow for localization of data with lower signal-to-noise and produce results that are more physiologically plausible when compared to single dipole results of discrete methods [50, 49]. The present study utilizes the linear minimum norm estimate method since it is most commonly used [51], produces good results when localizing distributed networks of brain activity seen in epileptic discharges, and is robust, allowing for statisti-
cal analysis and normalization of the cortical source distributions [53, 54, 3, 49]. Moreover, minimum-norm cortical source estimation is robust against error in the skull conductivity parameter of the forward model which is not a well known value [55].

The choice of head model is important to finding an accurate solution to the inverse problem. Realistic head models offer increased localization accuracy over simple shell models [56], and subject-specific realistic models have been shown to further increase accuracy in localizing epileptogenic zones in a case study of 152 patients [3]. Other studies have shown that modeling of basal source activity of temporal lobe epilepsy is optimized with the use of realistic forward models [57], and spherical models result in localization error of up to 30 mm in dipole localization. Moreover, spherical models typically result in the mislocalization of known mesial temporal lobe source activity to the frontal lobe [58, 59]. For this reason, subject-specific, realistic head models were used in the present study for HFA localization where individual MRI data was available. In patients for whom this data was not available, a realistic template, head model was used.

Artifacts originating from scalp muscles, eye blinks, eye movements, or patient movement often contaminate EEG recorded with conventional disk electrodes [60], and these artifacts greatly hinder the interpretation of recorded seizures when they occur at the time of seizure onset [61]. To make matters worse, tonic or tonic-clonic seizures are characterized by prominent muscle activity, increasing the effects of these high frequency artifacts [62]. In a previous study using five of the present nine patients, Besio et al. [9] found that the TCRE automatically attenuates myogenic activity and movement artifacts without the loss of information that is coupled with conventional artifact removal techniques in digital signal processing. This loss is often unavoidable in conventional EEG when electromyogram (EMG)
artifact is within the same frequency range as high frequency components of brain activity. It was also shown that high frequency brain activity was evident in the tEEG where it was undetected in conventional EEG, and its subsequent source estimation by electrode location was highly correlated with the diagnosed SOZ [9].

The present study attempts to extend those findings to a greater number of patients and perform more robust source localization of the HFA. In nine clinical epilepsy patients, HFA was recorded with tEEG and localized to the surface of realistic, 3D cortical models. HFA sources were found in the diagnosed SOZ/IZ of all nine patients. Eight of these patients were diagnosed with a focal SOZ based on conventional EEG, and in only three of them were HFA sources found outside of the diagnosed SOZ. These three patients were E, G, and I in Table 1.1. As shown in Figure 1.5, HFA sources were found in the left temporal and parietal regions of patient G, outside the diagnosed right frontotemporal SOZ. However, functional MRI of this patient revealed a tumor in the left temporal lobe, issues with the intensity of white subcortical and deep matter in the left temporal lobe, and destruction of fibers in the rostral portion of the uncinate fasciculus. In PET imaging, hypometabolism was found in the left temporal lobe, especially in the posterior inferior temporal gyrus. It’s possible that these conditions may explain the left hemispheric HFA sources found in this patient. Thus, HFA may prove to be a useful biomarker for other epileptic etiologies in addition to the clinical SOZ. For example, before the pathology of patient D progressed to a generalized, non-focal seizure onset, HFA was found locally in the left hemisphere. It was later revealed in MRI that this patient suffered from mesial temporal sclerosis in the left temporal lobe. Future studies should explore the validity of HFA found in tEEG as biomarkers for specific etiologies of epilepsy.

The other two patients (E, I) who experienced HFA sources outside of the
diagnosed SOZ did not suffer these other conditions to help explain such results. Sources of said activity were found in the left temporal and parietal SOZ of patient I in addition to the left occipital lobe. It is probable that the left occipital result is due to the proximity of the region to the SOZ. In the case of patient E, HFA sources were found in the left premotor SOZ as well as the surrounding brain regions and the contralateral hemisphere. Interhemispheric connections between the two motor regions could explain these results.

As noted in Besio et al. [9], a drawback of tEEG is the attenuation of signals of wide spatial distribution. While HFA biomarkers do not exhibit such a distribution, other important biomarkers such as spike-waves do [63]. Thus, it is important that tEEG recording be performed complimentary to conventional EEG in clinical practice. Fortunately, the outer ring of the TCRE has been shown to record signals equivalent to EEG [64]. In the previous study, it was shown that HFA found in tEEG were absent in EEG, but a one-to-one comparison of tEEG and EEG could not be made for all subjects in the present study because all EEG was recorded at 200 Hz. Additionally, not all data was saved such that emulated EEG (eEEG) by the outer ring could be used in its stead. Future studies should include identical recording parameters for tEEG and EEG for a more robust comparison.

Other possible sources of error include manual co-registration of electrode locations to the head models and the lack of a tEEG specific forward model. Exact locations of the electrodes were not measured or recorded. Therefore, a position digitizer would help localization in future efforts such that channel locations need not be placed manually on the head model. Increasing the electrode density and head coverage would also help in localization, as 19 channels per recording is sparse coverage. Song et al. [65] performed MNE and sLORETA source localization of epileptic spike activity with 32, 64, 128, and 256 channel upper head coverage and
whole-head coverage montages. They found poor results with less than 64 channels and asymptotic improvement above this number. Mis-localization was found in all sampling densities using only the upper head surface, and a 256 channel montage with a 2 cm intersensor distance over the entire head, upper and inferior surfaces, produced the best results [65]. Thus, the 19 channel, upper head montage used here is a major limiting factor. Future studies should explore the relationship of head coverage and number of tEEG channels used for localization. The improved spatial resolution of the TCRE would likely lead to less required channels to achieve an accuracy obtained from conventional EEG. It is also likely that a 256 channel, whole-head coverage montage would yield more accurate and focal results than the conventional EEG of the same montage.

Moreover, the development of a tEEG forward model is crucial to future source localization studies with the TCRE. Conceptually speaking, the inverse operator fits the forward model to the recorded data, calculating the maximum likelihood distribution of activation on the model to best explain the data. Currently, the forward solution for EEG is used for tEEG localization. Thus, source localization is calculated as if the recording is EEG, and its resulting magnitude should not be received with confidence because the inverse operator is calculating this value as if the inputs are surface potentials while they are actually potential differentials estimating the Laplacian. It is difficult to say exactly how a tEEG forward model would affect results. The effect would largely depend on the position of sources relative to the TCRE and their orientation with respect to the scalp surface (i.e. tangential or radial). Focality and magnitude of sources would likely be influenced by the model change, leaving the center location of found sources unchanged. It is the belief of the present authors that such a model would produce less spatially distributed results, improving the precision of tEEG source localization. Therefore,
future development of a tEEG forward model to study its influence on resulting sources is a paramount next step in tEEG source location research. Its implementation would require the forward model to be defined with sufficient resolution to determine potential differences between distances equal to TCRE ring spacing. Then lead field matrix values could be calculated using the nine-point-method as described in Besio et al. [22].

Despite these drawbacks, localization of HFA generators in tEEG was highly correlated with SOZ/IZ diagnoses. In each patient, HFA generators were found in the SOZ/IZ, and in only one patient were these generators found outside the SOZ without a strong physiological explanation. Additional evidence, although limited, also suggests that HFA in tEEG may prove to be useful biomarkers for determining underlying etiology of the epilepsy such as brain tumors and tuberous sclerosis. When compared to previously reported pathological HFOs [66, 67] and to non-pathological, normal physiological high frequency activity [68], the HFA reported here is much more narrowband. This spectral characteristic may prove to be a useful distinguishing feature for differentiating between pathological and non-pathological HFOs which is a major obstacle in the analytical use of HFOs in presurgical evaluation [69, 66].

Thus, the TCRE allows for noninvasive measurement of a unique HFA biomarker found in epilepsy patients and its subsequent localization. The HFA generators determined from tEEG appear to be highly correlated to clinically diagnosed SOZ/IZs. High frequency biomarkers are often too difficult to detect without invasive procedures, making source localization of tEEG measurements a possible solution to narrowing the probable regions of interest before such procedures and their inherent risks are introduced to patients.
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MANUSCRIPT 2

Source Localization of Event-Related Potentials in Tripolar Electroencephalography

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2.1 Abstract

Knowing where sources of activity are located in the brain can help with diagnosis and brain-machine interfaces. Locating the sources of electroencephalography (EEG) signals acquired on the scalp is an ill-posed problem since an infinite number of inverse configurations can result in the same potential distribution on the head surface. Therefore, additional constraints to the source space must be used to find a unique solution. Distributed source methods constrain the source space to a large number of dipoles distributed either on the cortical surface or within the brain. These methods are underdetermined and result in a blurring of the source space. In the present study, the increased spatial resolution of tri-polar EEG (tEEG) was used to minimize this blurring with respect to the sources of event-related potentials (ERPs). Visual evoked potentials (VEPs) (n=4) and movement-related potentials (MRPs) (n=4) were recorded in both EEG and tEEG concurrently; tEEG produces significantly more focal localization of each ERP.

2.2 Introduction

It can be advantageous to locate sources of brain activity measured with electroencephalography (EEG) for clinical diagnosis and brain-machine interface (BMI) purposes. In epilepsy patients who suffer from focal seizure onset, the seizure onset zone (SOZ) can be identified with EEG source localization (ESL) and surgically removed with good therapeutic effect [1]. Additionally, specific cortical regions important for neurofeedback devices or prosthetic control can be identified with ESL. For cortical implants or other invasive BMI, ESL can aid in identifying regions of interest before invasive methods are employed. Such procedures, including invasive EEG (iEEG), are associated with risks to patients including transient and permanent neurologic deficits, infections, hematoma, non-habitual seizures, cerebral infarction, cerebral edema, and increased intracranial pressure.
Therefore, a better understanding of individual anatomy is indicated. Consequently, there exists a need to accurately identify cortical sources of EEG activity measured on the scalp surface.

ESL is fundamentally broken into the forward and inverse problem when determining cortical sources of signals measured on the scalp surface[4, 5]. Identification of the source from signal is the inverse problem. The forward problem is the propagation of signals from source to the scalp surface, and its solution, the forward model, is necessary to solve the inverse problem [6]. Specifically, the head model used and its compartments, surfaces, and conductivities, also known as the volume conductor, comprise the forward model [4].

The inverse problem is ill-posed since an infinite number of source configurations can result in the same potential distribution on the head surface. Therefore, additional constraints to the source space must be used to find a unique solution. Distributed source methods constrain the source space to a large number of dipoles distributed either on the cortical surface of, or within the brain model, but they yield an underdetermined solution. Used with conventional EEG and its limited spatial resolution, these localization methods produce poor resolution. However, distributed source methods allow for localization of data with lower signal-to-noise and produce results that are more physiologically plausible when compared to single dipole results of discrete methods [5, 7]. The present study utilizes the linear minimum norm estimate method since it is most commonly used [4], produces good results when localizing distributed networks of brain activity, and is robust, allowing for statistical analysis and normalization of the cortical source distributions[1, 5, 8, 9]. Moreover, minimum-norm cortical source estimation is robust against error in the skull conductivity parameter of the forward model which is not a well known value[10].
Tripolar EEG (tEEG), EEG recorded with the tripolar concentric ring electrode (TCRE) (Figure 2.1) has increased signal-to-noise ratio (SNR) and spatial resolution [11, 12, 13, 14]. The novelty of the TCRE design and instrumentation is that two bipolar signals are recorded from three closely spaced, concentric electrode elements. Then the tripolar Laplacian derivation, first described in Besio et al. [11], is estimated as the weighted sum, $16(M-D)-(O-D)$, where $O$, $M$, and $D$ are the potentials on the outer ring, middle ring, and central disc of the TCRE, respectively. When compared with conventional EEG signals, signals recorded with the TCRE have shown a 6.25 dB increase in signal-to-noise ratio (SNR) and less than one-tenth (8.27%) the mutual information between a pair of adjacent electrodes [11, 14]. Thus, a main drawback of conventional EEG, poor spatial resolution, is vastly improved upon in tEEG and leads the present authors to believe the focality of distributed source results can be improved with tEEG.

![Figure 2.1. Conventional disc electrode (A) and tripolar concentric ring electrode (B).](image)

In this study, event-related potentials (ERPs) were used as test signals for evaluating this hypothesis. ERPs are small voltages generated in the brain in response to specific events or stimuli [15]. These EEG signals are time locked to sensory, motor, or cognitive events. They arise from the summed activity of
postsynaptic potentials produced from pyramidal neurons firing in synchrony while processing information pertinent to the event [16]. ERP components are typically named by the sign of the potential followed by the latency (ms) with respect to stimulus or the ordinal position in the ERP. Here, two types of ERPs are used to explore tEEG source localization: movement related potentials (MRPs), also known as movement related cortical potentials (MRCPs), and visual evoked potentials (VEPs).

VEPs elicited by pattern reversal (i.e. checkerboard) are characterized by an initial negative component peaking at approximately 75 ms after stimulus (N75) followed by a positive component at around 100 ms (P100) and another negative component at around 145 ms (N145) [17]. Several studies suggest that the neural generators of the N75 and P100 components are in the primary visual cortex (area V1) [18, 19, 20, 21, 22, 23]. Di Russo et al. [24] confirmed these results in a source localization study of the early components of VEPs elicited by pattern-reversal gratings in 25 subjects. They combined scalp recordings of VEPs and discrete source dipole modeling with functional magnetic resonance imaging (fMRI) and retinotopic mapping, restricting the source space to areas in which activations were apparent in the fMRI. Interestingly, the second component was found at around 125 ms instead of 100 ms, but the generators of the first and second components were both determined as dipoles seeded in the V1 region.

MRPs are potentials that occur in close temporal relation to movement or imagined movement and may occur before, during, or after the movement. Kornhuber and Deeke were the first to measure MRP components that occur before movement and distinguished four components: the Bereitschafts potential (readiness potential), pre-motion positivity, motor potential, and reafferent potential [25]. Since, several studies characterized different components of MRPs but the
consensus among them is that movement is preceded by the readiness potential, a negativity observed as early as 2 s before movement onset in the pre-supplementary motor area (pre-SMA) with no site-specificity and in the SMA proper according to the somatotopic organization, and shortly thereafter in the lateral premotor cortex bilaterally with clear somatotopy. About 400 ms before movement onset, a steeper negative slope occurs in the contralateral primary motor cortex (M1) and lateral premotor cortex with precise somatotopy [26, 27, 28]. The readiness potential is followed by a negativity called the initial slope of the motor potential (isMP) that occurs just prior movement at around -10 ms and during movement in the region of the primary motor cortex (M1) that corresponds to the movement site [26, 29]. Several post movement components have been identified. Shibasaki et al. [30] distinguished N50, P90, N160 and P300 components when studying hand movements. The N50 component, or frontal peak of the motor potential (fpMP) is a negative peak localized to the contralateral, frontal region of the primary motor cortex [30, 29]. Other generators of post movement components have been localized to the posterior parietal cortex [30, 31]. The P300 component is the reafferent potential distinguished by Kornhuber and Deeke [25].

This study seeks to localize ERPs in healthy participants to realistic cortical models with the goal that tEEG allows for more focal localization than conventional EEG in distributed source imaging methods. More precise source localization with tEEG signals would increase proficiency in determining areas of interest in BMI and diagnosis while limiting surgical risks.

2.3 Methodology
2.3.1 Data Acquisition

For each part of the study, subjects (male: n=3, female: n=1) were volunteers who gave informed consent, and the experiments were conducted in accordance
with the IRB approved protocol (HU0809-45). All four right handed subjects involved in the experiment were free of any known neurological disorders and their age ranged from 20 to 28 years. The tEEG and emulated EEG (eEEG) data, outer TCRE disc recording shown to emulate conventional EEG [32], were concurrently collected using a Neuroscan Synamps RT amplifier sampled at 500Hz with the Curry 8 software. Due to amplifier limitations, electrodes were placed on 16 of the standard 10-20 locations, excluding A1, A2, F7, F8, and T4. A gain of 187.5 was applied to the tEEG signal from the CREmedical preamplifier.

For MRP measurements, a hospital push button was modified to send a transistor-transistor logic (TTL) pulse to the amplifier at each button press to time-mark the data. The software was set to notify the experimenter once 350 presses were obtained at which the recording was stopped. The participant was seated in a comfortable chair and asked to press the hospital push button at their own pace, with the instruction to press no faster than once per 2 seconds.

For VEP measurements, the stimulus was a reversing checkerboard which reversed polarity at a rate of 1.93Hz. The checkerboard was setup with each check equivalent to 1 degree of arc and the whole screen subtending 20 degrees of arc. The participant was seated 70 cm from the monitor and asked to focus on a red dot in the center of the checkerboard during the stimulation. The experiment was set up so that the checkerboard reversed 10 times and then paused for 10s. It was repeated for 5 minutes, and the participant was given a 60 second break. After the break, the 5-minute stimulus paradigm was repeated two more times for a total of 3 sets with 200 stimuli each, resulting in 600 recorded stimuli.

2.3.2 Signal Processing and Localization

Data was imported into EEGLab, a freely available (https://sccn.ucsd.edu/eeglab/) plugin for MATLAB. Recordings were de-trended to remove DC bias
and a low-pass, non-causal, IIR Butterworth filter (6th order) with a 40 Hz half-amplitude cutoff was applied forward and backward for zero phase. Noisy channels were removed before segmenting the data into single trial epochs. MRP recordings were segmented into 1 second epochs centered at the button press (t = 0 ms), and VEP recordings were segmented into 0.5 second epochs with 100 ms pre-stimulus (t = -100 to 0 ms) and 400 ms post stimulus (t = 0 to 400 ms). Epochs containing artifacts such as EOG activity were eliminated with a peak-to-peak threshold. The threshold was determined empirically for each recording. Data was then imported into Brainstorm [33], which is a freely available (http://neuroimage.usc.edu/brainstorm/), open-source application for the analysis of MEG, EEG, fNIRS, ECoG, and other brain recordings.

In Brainstorm, surface potentials of the average ERPs were localized to the surface of the ICBM152 head model. This model is derived from a non-linear average of MRI scans of the 152 subjects in the MNI152 database [34, 35]. A whitened and depth-weighted linear L2-minimum norm estimates (MNE) algorithm [5] was used to localize signals to a source space of dipoles constrained normal to the cortical surface of the model, resulting in current density plotted on the model cortical surface. For a full description of this localization method, please refer to the MNE manual [7], section 6, "The current estimates" which is available for download (http://www.martinos.org/meg/manuals/MNE-manual-2.7.pdf).

2.3.3 EEG vs. tEEG focality

To access the focality of tEEG localization results compared to that of eEEG results, the number of dipoles above % thresholds were counted in each result for every trial. Each vertex within the resulting boundary element method (BEM) model represents a dipole and is assigned a current density value. Thresholds of 10 to 90 % were tested in increments of 10 %. 100% represents the single
trial maximum. Thus, a lower number above threshold would indicate a more focal localization result. For each threshold, the average number above threshold among trials was calculated and a t-test \((p < 0.05)\) was used to determine significant difference between eEEG and tEEG focality.

### 2.3.4 Signal-to-noise ratio

The relationship between number of N-trials and SNR was studied in eEEG and tEEG. Random sets of N-trials were used for SNR calculation in dB with the equation

\[
SNR_{\text{dB}} = 10 \log_{10} \frac{\sigma_S^2}{\sigma_Q^2}
\]

where \(\sigma_S^2\) is the variance of the signal data and \(\sigma_Q^2\) is the variance of the noise data.

For each of the N-trials \((N=10, 20, 30, \ldots, 150)\), 100 iterations of uniform, randomly sampled trials were used for SNR calculation. SNR was then averaged among iterations. Each iteration was used as a data point for the two-sample t-test \((p < 0.05)\) comparison between eEEG and tEEG SNR. The higher SNR between channels P3, Pz, P4, O1, and O2 was used for VEP recordings, and the higher SNR of C3 and Cz was used for MRPs. Noise in the VEP experiments was determined by the 100 ms window before stimulus, and it was determined by the -500 to -300 ms window in the MRPs. Signal was determined by the 100 ms to 200 ms window for VEPs and -100 ms to 300 ms window for MRPs.

### 2.4 Results

Movement-related and visual evoked potentials were recorded with tEEG and eEEG simultaneously with TCREs in four healthy subjects. For each ERP and measure, the SNR was determined as a function of number of trials. ERP peaks were localized and their focality was compared between measures by counting
number of BEM model elements above threshold.

2.4.1 MRP Localization

Surface potentials related to right thumb presses were localized to the left motor region of all four subjects. Figure 2.2 shows a representative example of the average MRP recorded with eEEG (Figure 2.2a) and tEEG (Figure 2.2b) in one subject. In all subjects, the largest peak was the positive potential found at approximately 200 ms post press. This is the peak that was localized and for which focality was determined. Figure 2.2c and 2d are the respective localization results for the eEEG and tEEG shown in Figure 2.2a and 2.2b. The results are visually more localized to the left motor region in the tEEG, while the localization of eEEG is more spatially distributed around the left motor and central regions. For three subjects (including the subject depicted in Figure 2.2), the tEEG localization results were significantly more focal ($p < 0.05$) for all thresholds. In the remaining subject (D), the tEEG results were significantly more focal ($p < 0.05$) for all thresholds except 60% and 70% for which there was no significant difference in focality. Table 2.1 shows the $p$ values for each subject comparison of tEEG to eEEG MRP focality.

| Threshold (%) | Subject A   | Subject B   | Subject C   | Subject D   |
|---------------|-------------|-------------|-------------|-------------|
| 10            | 1.48E-43    | 4.87E-159   | 5.77E-43    | 5.06E-45    |
| 20            | 5.52E-27    | 7.58E-86    | 6.20E-16    | 1.02E-17    |
| 30            | 3.32E-19    | 4.62E-46    | 6.13E-08    | 1.69E-08    |
| 40            | 3.82E-14    | 1.13E-27    | 7.51E-05    | 2.06E-4     |
| 50            | 5.93E-10    | 4.26E-19    | 4.96E-04    | 1.88E-02    |
| 60            | 1.08E-06    | 3.39E-13    | 1.34E-03    | 4.65E-01    |
| 70            | 7.01E-05    | 2.22E-12    | 3.31E-03    | 4.42E-01    |
| 80            | 4.65E-02    | 3.96E-21    | 1.23E-05    | 7.58E-03    |
| 90            | 4.42E-02    | 5.15E-41    | 5.71E-13    | 4.52E-09    |
Figure 2.2. The average MRP for a representative subject recorded with eEEG (a) and tEEG (b). MNE localization of the positive peak approximately 200 ms post button press found in eEEG (c) and tEEG (d).
2.4.2 MRP Signal-to-noise

SNR was calculated as a function of number of trials for each subject and shown in Figure 2.3 for tEEG (green) and eEEG (blue). For N-trials less than 60 the tEEG SNR was significantly higher ($p < 0.05$) than eEEG in three of the subjects (Figure 2.3a, 2.3b, and 2.3d). As N-trials increased, the SNR of tEEG and eEEG became more similar for these three subjects. SNR of tEEG was significantly higher for all N-trials in one of the subjects (Figure 2.3a) and for all N-trials except 100, 120, 130, 140, and 150 for another (Figure 2.3b). The subject depicted in Figure 2.3c showed significantly higher SNR in eEEG for most N-trials with only $N = 20$ for which tEEG SNR was significantly higher.

2.4.3 VEP Localization

Surface potentials related to a reverse checkerboard stimulus were localized to the parieto-occipital region of all four subjects. Figure 2.4 shows a representative example of the average VEP recorded with eEEG (Figure 2.4a) and tEEG (Figure 2.4b) in one subject. In all subjects, the largest peak was either the first negative component at approximately 100 ms post reversal or the positive potential found at approximately 150 ms. The largest peak for each subject was localized and used to measure focality. This peak was the same in eEEG and tEEG for each subject. Figure 2.4c and 2.4d are the respective localization results for the eEEG and tEEG shown in Figure 2.4a and 2.4b. The results are visually more localized to the parieto-occipital region in the tEEG, while the localization of eEEG is more spatially distributed. For this subject, the tEEG results were significantly more focal ($p < 0.05$) for all thresholds except 40%, 50%, 60%, and 70% for which there was no significant difference. In two of the other subjects, tEEG results were significantly more focal for all thresholds, and tEEG results were significantly more focal for all threshold except 90% (no significant difference) in the remaining
Figure 2.3. Signal-to-noise ratio of MRP recorded with tEEG (green) and eEEG (blue) as a function of number of trials. An asterisk (*) indicates significant difference (p < 0.05) between tEEG and eEEG at the respective number of trials.
subject. Table 2.2 shows the p values for each subject comparison of tEEG to eEEG VEP focality.

| Threshold (%) | Subject A     | Subject B     | Subject C     | Subject D     |
|---------------|---------------|---------------|---------------|---------------|
| 10            | 2.80E-64      | 1.00E-19      | 2.13E-39      | 3.57E-25      |
| 20            | 6.30E-49      | 1.32E-05      | 2.59E-24      | 1.12E-15      |
| 30            | 1.88E-43      | 7.88E-03      | 3.70E-17      | 5.7E-14       |
| 40            | 7.98E-38      | 7.64E-02      | 6.25E-14      | 9.53E-13      |
| 50            | 3.30E-30      | 1.05E-01      | 7.62E-13      | 4.87E-11      |
| 60            | 1.52E-23      | 1.45E-01      | 1.23E-11      | 7.30E-09      |
| 70            | 1.03E-17      | 1.83E-01      | 1.36E-11      | 2.00E-07      |
| 80            | 5.7E-09       | 2.09E-02      | 8.85E-14      | 2.08E-09      |
| 90            | 6.12E-01      | 4.62E-03      | 1.01E-11      | 1.91E-10      |

### 2.4.4 VEP Signal-to-noise

Figure 2.5 shows the VEP SNR for tEEG (green) and eEEG (blue) as a function of number of trials. For all cases of significant difference (p < 0.05), the VEP SNR of eEEG was higher than that of tEEG. There was no significant difference for 10 and 20 trials in two of the subjects (Figure 2.5a and 2.5d).

### 2.5 Discussion

Precise source localization remains a problem for noninvasive brain measures, such as EEG, due to poor spatial resolution. Laplacian estimation with tEEG aims to improve spatial resolution, lending itself to more focal localization results with dipole modeling methods. The Laplacian attenuates potential distributions on the scalp with low spatial frequency. Signals that originate from further away are blurred by volume conduction, decreasing spatial frequency on the scalp and eliciting attenuation in tEEG. Likewise, signals from sources near a TCRE produce a greater spatial frequency across the scalp beneath the electrode, resulting in amplification.

ERPs were used as test signals to study the influence of Laplacian estimation.
Figure 2.4. The average VEP for a representative subject recorded with eEEG (a) and tEEG (b).
Figure 2.5. Signal-to-noise ratio of VEP recorded with tEEG (green) and eEEG (blue) as a function of number of trials. An asterisk (*) indicates significant difference (p < 0.05) between tEEG and eEEG at the respective number of trials.
by tEEG on distributed source imaging methods. Movement-related potentials and visual evoked potentials were recorded with eEEG and tEEG simultaneously in four healthy subjects. Due to artifact found at $t = 0$ in the eEEG MRP recordings (shown in channels F3 and Fz in Figure 2.2a), post movement MRP components were used for focality comparison. This artifact was found in different channels between subjects. Interference from the push button cable may be the source of these artifacts as the channel locations affected do not appear to be related to a physiological process. They also do not appear to contaminate the VEP recordings.

The localization of MRPs were significantly more focal (Table 2.1) for all thresholds and subjects except for two thresholds in a single subject. As expected, potentials related to the right thumb movement were localized to the motor region of the left hemisphere on both the pre- and post-central gyrus. Notwithstanding the limited coverage of a 16-channel montage, it is theorized a higher density electrode cont may allow for precise localization of the motor potential to the primary motor cortex on the pre-central gyrus or post-movement components to corresponding primary motor and parietal regions. Pending the degree of precision, it may even allow for improved, noninvasive BMI devices for movement which typically require invasive measurements.

SNR of ERPs increases with the number of trials, and it was measured as a function of N-trials for comparison between eEEG and tEEG. For three of the four subjects, MRPs measured by tEEG had a higher SNR where there was a significant difference. This significance was present for most N-trials in two subjects. In one subject (subject C), the SNR of MRPs recorded in eEEG was significantly higher for most N-trials. While significance in difference was not tested between subjects, the SNR of the MRPs recorded in this subject with eEEG was higher for $N < 50$ when compared to the other three subjects. Typically, noise attenuation
allows the TCRE a greater SNR [11, 12, 13, 14], and more trials are needed to average out noise for conventional EEG to attain a similar SNR, as is seen in the present findings. With increased N-trials, the difference between eEEG and tEEG SNR diminishes. However, in subject C, the SNR in eEEG was higher for lower N-trials. Inter-subject variability in anatomy could explain these results, i.e. a tangential cortical source in a sulcus results in a lower spatial frequency at the nearby scalp surface. It is possible that the MRP generators of this subject are deeper in the sulcus than is typical with movement. Moreover, if the TCRE was placed further away from MRP cortical generators than the other subjects, then the Laplacian estimation would attenuate the signal, yielding a lower SNR for tEEG when compared to eEEG.

Like the MRPs, VEP localization was more focal with tEEG than eEEG (Table 2.2) in all cases of significant difference (all but five subject-threshold pairs). However, in both tEEG and eEEG, the VEPs were localized to parieto-occipital regions instead of the expected primary visual cortex. This is almost certainly due to the montage and sensor density configuration. The higher VEP SNR in eEEG across all subjects indicate the TCRE placement was not optimal for recording VEPs, causing Laplacian attenuation of the signal. Of the locations used, the O1 and O2 channels were the only two near V1. These two channels were also on the bounding edge of the montage, making correct localization difficult. Full electrode coverage over a signal source is crucial to correct localization. Song et al. [36] performed MNE and sLORETA source localization of epileptic spike activity with 32, 64, 128, and 256 channel upper head coverage and whole-head coverage montages. They found poor results with less than 64 channels and asymptotic improvement above this number. Mis-localization was found in all sampling densities using only the upper head surface, and a 256 channel montage with a 2 cm intersensor dis-
tance over the entire head, upper and inferior surfaces, produced the best results [36]. Thus, the 16-channel, upper head montage used here was not optimal for VEP localization.

For correct VEP localization a greater density of channels around the primary visual cortex should be used, and present work is limited by sparse electrode density and limited head coverage. In contrast, the correct localization of MRPs is likely due to more adequate coverage of the motor cortex which resides closer to the center of the montage. Another present limitation includes manual co-registration of electrode locations to the head models. Exact locations of the electrodes were not measured or recorded. A position digitizer would help localization in future efforts.

Additionally, a tEEG forward model was not used, and its development should be the focus of future source localization studies with the TCRE. Conceptually speaking, the inverse operator fits the forward model to the recorded data. Currently, the forward solution for EEG is used for tEEG localization. Thus, current sources are calculated as if the recording is EEG, and its resulting magnitude should not be trusted due to differences in EEG and tEEG magnitude. The impact of a tEEG forward model would largely depend on the position of sources relative to the TCRE and their orientation with respect to the scalp surface (i.e. tangential or radial). Focality and magnitude would better reflect true sources. Such a model would possibly produce less spatially distributed results, further improving the precision of tEEG source localization. In this study, it is unlikely that the lack of a tEEG forward model explains the mislocalization of VEPs since this error was found in eEEG as well.

With only four subjects substantial conclusions on the improved focality of tEEG source localization are limited. However, these findings are evidence for the
potential of tEEG and indicate that high density tEEG recordings with proper montages would yield even more precision when compared to other noninvasive measures. The choice of montage is critical for tEEG recordings. If high density montages are not feasible, then complete coverage around the source region is necessary for correct localization. Moreover, a higher SNR can be obtained with ERPs in fewer number of trials, but this is highly sensitive to montage choice. If electrode locations over the source are not used then the Laplacian estimation in tEEG will attenuate the signal as shown here with VEPs. Assuming an adequate montage, this advantage can be helpful in clinical settings where obtaining many trials is difficult.

Consequently, future studies should focus on the development of a tEEG forward model for source localization and investigate its influence on localization. Based on the present findings, these studies could show great improvements in localization precision. The increased spatial resolution of the TCRE lends itself to higher gains in precision for montages above 64 channels than found in Song et al. [36]. In clinical applications where locating sources of brain activity is important for diagnosis, tEEG shows potential for precise identification of sources noninvasively, reducing risk in patient care.

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APPENDIX A
Background Material

A.1 Abstract

This appendix provides additional background to the material presented in Manuscripts 1 and 2. The topics of epilepsy, electroencephalography (EEG), tripolar EEG (tEEG), EEG source localization (ESL), and event-related potentials (ERPs) are discussed.

A.2 Epilepsy

Epilepsy is a neurological disorder characterized by a predisposition to generate epileptic seizures and the ensuing neurobiological, cognitive, psychological, and social consequences. Abnormal excessive or synchronous neuronal activity in the brain cause clinical manifestations that make up epileptic seizures, and the areas of cortex that are responsible for their generation are termed epileptogenic zones [1]. The disorder affects approximately 70 million people worldwide [2] and nearly 2.5 million Americans with the highest incidence rates in young, neonatal patients and elderly individuals over the age of 75 years [3]. In the United States alone, there are approximately 200,000 new cases of epilepsy each year, and estimated yearly costs from epilepsy and seizures have reached 12.5 billion dollars [3].

Seizures can be caused by severe metabolic disturbance, head trauma, alcohol intake and withdrawal, fever, illness, and some medications. A variety of factors can also induce epilepsy, including traumatic brain injury, stroke, tumor, central nervous system infection, inflammation or autoimmune diseases, genetic mutations, and structural brain abnormalities such as sclerosis, cortical dysplasia, and vascular malformation [3]. Each of these instances can result in the hyperexcitability found in epilepsy. Most theories of the underlying mechanisms of the disease fo-
cus on increased excitability and/or decreased inhibition of neuronal populations. To understand them, one must be familiar with the physiology governing neuron excitability and signaling.

Action potentials are the mechanism by which a signal travels through a neuron, and synaptic transmission is the main mechanism of communication between neurons. The action potential is a transient depolarization of a neuron from its negative resting potential to a positive spike. This spike propagates down the neuronal axon by voltage-gated ion channels. Inward Na+ ion current and outward K+ ion current are the main contributors to the positive spike generation and following negative hyperpolarization, respectively. These action potentials signal for the release of neurotransmitters from the axon terminal which then bind to ionotropic receptors on the postsynaptic neuron. Neurotransmitter receptors are ligand-gated ion channels that activate upon binding, allowing for subsequent hyperpolarization or depolarization of the cell. The major neurotransmitters in the brain are glutamate, gamma-amino-butyric acid (GABA), acetylcholine (ACh), norepinephrine, dopamine, serotonin, and histamine [4].

Glutamate is the major neurotransmitter involved in excitatory neurotransmission, and there are several subtypes of ionotropic glutamate receptors. They can be found on excitatory principal cells, inhibitory interneurons, and certain types of glial cells [4]. The ionotropic glutamate receptor subclasses are the alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) receptor, kainate receptor, and N-methylD-aspartate (NMDA) receptor which are differentiated from one another by cation permeability and sensitivity to pharmacological agonists/antagonists. All ionotropic glutamate receptors are permeable to Na+ and K+, and it is the influx of Na+ and outflow of K+ through these channels that contribute to membrane depolarization and subsequent action potential. The
NMDA receptor also has a Ca++ channel that is blocked by Mg++ ions in the resting state. After local membrane depolarization, Mg++ is displaced and the channel becomes permeable to Ca++. Influx of Ca++ further depolarizes the cell and is thought to contribute to Ca++ mediated neuronal injury during excessive neuronal activation, potentially leading to cell death, a process termed excitotoxicity [4]. NMDA, AMPA and kainite receptor agonists have been found to induce seizure activity in animal epilepsy models, and their antagonists suppress seizure activity.

GABA is responsible for inhibitory neurotransmission and binds with two ionotropic receptor subtypes. GABA_A receptors are found in the post-synapse and they activate inward Cl- currents that hyperpolarize the cell and inhibit action potentials. GABA_A receptor agonists generally suppress seizures. In contrast, GABA_B receptors are found on the pre-synapse. They modulate neurotransmitter release via second-messenger systems that often lead to K+ channel activation and subsequent hyperpolarizing outward K+ current [4]. Because neural networks of the brain are complex one cannot simply conclude that increase in glutamate transmission or decrease in GABA transmission will result in hyperexcitability or seizures. Some principal neurons may signal for the activation of inhibitory networks and an increase in their activity would likely not result in epileptic activity. In the same network, loss of glutamate transmission would decrease GABA inhibition downstream and could result in hyperexcitability of networks normally inhibited by the affected interneurons. While some networks have been widely studied and understood, (i.e. hippocampal pathways), many are not and it is often unclear if a case of epilepsy is caused by GABA or glutamate dysfunction. The mechanisms underlying generalized seizures, seizures that arise from widespread cortical areas, are still uncertain. Generally true with all cases, however, is an
abnormal imbalance of excitation and inhibition [4].

Focal seizure initiation is characterized by synchronous, high-frequency bursts of action potentials of a neuronal population. This bursting is a result of prolonged depolarization and subsequent activation of Ca++ channels and their inward current. In turn, voltage-gated Na+ channels open, generating repetitive action potentials. This hyperactivity can recruit the activation of surrounding neuron networks or even more distant networks via long association pathways, allowing the seizure to propagate. While inhibitory interneurons can typically prevent networks from recruiting surrounding areas, bursting leads to an increase in extracellular K+, making hyperpolarizing K+ outward currents less effective. Moreover, Ca++ accumulates in the presynaptic terminals, enhancing neurotransmitter release, and NMDA receptor activation exacerbates the prolonged depolarization by increasing inward Ca++ current. Most seizures will spontaneously terminate after seconds or minutes, but in some cases, such as status epilepticus, they do not terminate within 5 minutes of onset and the resulting excitotoxicity can be life-threatening.

Correct diagnosis and seizure control are crucial for improving quality of life in patients with epilepsy. Diagnostic tools such as electroencephalography (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), and neuropsychiatric testing are used to help clinicians identify a patient’s seizure type and underlying etiology [3]. Epileptiform discharges in EEG help in diagnosis and sources of high frequency biomarkers are indicative of seizure generating tissue. Antiepileptic drugs (AEDs) are generally the first line of treatment for patients with epilepsy. They aim to maximize seizure control while minimizing adverse drug effects in a number of mechanisms which include blocking Na+ currents, enhancing GABA-mediated Cl- currents, blocking calcium currents, and/or
blocking glutamate-mediated currents [4]. However, these drugs have a narrow therapeutic window, making seizure prevention without toxicity or side effects difficult. Adverse effects can include fatigue, dizziness, tremor, Paresthesia, Diplopia or blurred vision, cognitive and motor impairment, mood changes, changes in sexual function, weight gain, and nausea [4].

A pharmacological approach is not always feasible for seizure control. Medically intractable or refractory epilepsy is defined as a failure of two adequate trials of AED treatment. Approximately one third of patients with epilepsy are refractory to AEDs [3]. For these patients, non-pharmacological treatments such as epilepsy surgery, neurostimulation therapy, and diet therapy are considered. Vagus nerve stimulation (VNS), responsive neurostimulator (RNS) therapy, and ketogenic diets have all shown some degree of success for seizure control, but among refractory epilepsy patients, epilepsy surgery is most commonly considered if there is a focal seizure onset zone (SOZ) that is amenable to resection [3]. EEG then plays an important role in presurgical evaluation. Long term video-EEG monitoring is used to confirm the diagnosis and type of focal onset by identifying the sources of SOZ biomarkers such as epileptiform discharges, interictal spikes, and high frequency oscillations (HFOs). Accurate localization of the focal SOZ is crucial for successful surgical resection and subsequent seizure control. Thus, subdural electrodes and depth electrodes are often used for invasive EEG to better define areas for resection and areas of eloquent cortex that must be left intact [5, 6, 7].

A.3 Electroencephalography

Electroencephalography (EEG) was first studied in 1875 by English physician Richard Caton on monkeys and rabbits. In 1924, Hans Berger invented the first EEG device from radio equipment and was the first to study human EEG [8]. Pyramidal cells of the cortex are the main contributors of this activity. These
cells have long apical dendrites and are generally oriented such that they extend from the cell body towards the cortical surface. EEG measures the electrical potentials that arise from extracellular post-synaptic currents. Consider neuronal excitatory signaling. Excitatory post-synaptic potentials (EPSPs) arise from positively charged ions entering the cell, leaving a relatively negative charge in the extracellular space near the synapse. The inward positive current flows through the dendrite and eventually moves outward across the cell membrane further from the synapse, creating a relatively positive charge in the extracellular space. The positive and negative regions outside the dendrite make the dipole that contributes to EEG. Its measured polarity depends on the orientation of the cell with respect to the scalp and the location of the EPSP on the cell. If the EPSP occurs closer to the cell body, then the positive region will be closer to the scalp. If the EPSP site is at the dendritic synapse of the apical dendrite, then the negative region will be closer to the scalp. Additionally, an inhibitory post-synaptic potential reverses this polarity due to negatively charged inward cellular currents [9].

To measure these dipoles, the potential must reach the scalp. Volume conduction is the mechanism by which these signals propagate through brain tissue. Ions repel nearby ions of like charge and those ions in turn repel others, resulting in the propagation of charge through the extracellular space. The signal must then pass through the dura, skull, and scalp layers to reach the electrode, but ions cannot pass from one layer, or volume, to another, so another mechanism is required. The dielectric boundary between volumes is an insulating layer and acts as a capacitor. Ions build up on the other side of the boundary as volume conduction pushes ions to the limits of the previous layer. Volume conduction is then responsible for the propagation of the ions through the subsequent layer. The layers from the brain to the dura layers, skull layers, scalp layers, electrode gel or paste, and electrode
form a series of conductive volumes and insulating layers [9].

The dipole of a single neuron post-synaptic potential is not sufficient to travel through these layers. The synchronous activity of many similarly oriented neurons is needed. Electrodes detect the sum of nearby charges, and the dipoles from multiple neurons in close proximity sum together. Therefore, ensembles of neurons must fire synchronously and sum to produce a large enough signal to detect at the scalp. Moreover, the neurons must be oriented similarly, or their dipoles will cancel each other out in summation [9]. An electrode’s detection of summed charges also leads to the greatest disadvantage of scalp EEG. The measured voltage reflects the sum of all charged ions influencing the electrons in the electrode, and the measurement at any position on the scalp will reflect the sum of many electric fields in the brain. Each dipole ensemble will influence ions in nearly all directions and, thus, have influence on the measurement in a range of scalp locations. The result is spatial smearing of the signal due to volume conduction. Thus, while EEG has many advantages including low cost, minimal risk, good temporal resolution, and ease of use, it suffers from poor spatial resolution due to this smearing. It also has lower signal-to-noise ratio than invasive methods and struggles to detect activity from deep brain structures.

A.4 Tripolar Electroencephalography

Spatial filters, such as surface Laplacian montages, aim to increase the spatial resolution of EEG. The surface Laplacian approximates the second spatial derivative of the potential distribution on the scalp [10]. In a Laplacian montage, each channel represents the difference between an electrode and a weighted average of the surrounding electrodes, effectively reducing the volume of source space over which each electrode averages [11]. Surface Laplacians act on the spatial distribution of potential on the scalp and emphasize distributions of higher
spatial frequencies while attenuating more widespread coherent signals. Smaller, nearby sources produce higher spatial frequencies near the recording site, while large or further away sources produce lower spatial frequency distributions near the electrode. Thus, the Laplacian is preferentially sensitive to localized, superficial sources that originate close to the observation point. Moreover, cortical patches parallel to the scalp surface that sit on gyri, radial sources, contribute more to the Laplacian than tangential sources which lie deeper in sulci.

In conventional EEG, large cortical sources contribute more to resulting scalp distributions which is characterized as a preferential sensitivity to low spatial frequency components of the source distribution [12, 11]. The selective sensitivity of the surface Laplacian to smaller source regions is due to its preferential sensitivity to higher spatial frequencies but is limited by the separation distances between electrodes and between sources and electrodes [13]. In other words, scalp potentials seen in EEG are a spatially low-pass filtered representation of the source distribution, and surface Laplacians are effectively spatially band-pass filtered representations of source distributions.

The surface Laplacian served as the motivation for the development of the tripolar concentric ring electrode (TCRE) by Dr. Walter Besio in 2006. The electrode consists of three concentric, conductive rings in a bullseye configuration. The novelty of the TCRE design and instrumentation is that two bipolar differential signals are recorded from three closely spaced, concentric electrode elements. Then the tripolar Laplacian derivation, first described in Besio et al. [14], is estimated as the weighted sum, \(16*(M-D)-(O-D)\), where O, M, and D are the potentials on the outer ring, middle ring, and central disc of the TCRE, respectively. This weighted sum approximates a focal Laplacian at the electrode site. Because the three rings are spaced in the same area as a conventional disc electrode, the TCRE
is not limited by electrode spacing like traditional Laplacian montages. Thus, it is able to select for nearby sources of activity while attenuating more distributed signals such as further away sources. Noise such as electromyogram (EMG) activity is also typically measured by each concentric ring equally and then attenuated by subtraction in the tripolar weighted sum. When compared with conventional EEG signals, signals recorded with the TCRE have shown a 6.25 dB increase in signal-to-noise ratio (SNR) and less than one-tenth (8.27%) the mutual information between a pair of adjacent electrodes [14, 15]. Most importantly, tripolar electroencephalography (tEEG), i.e., EEG recorded on the scalp with TCREs, has been found to detect high frequency biomarkers of epilepsy [16]. These biomarkers are localized, high frequency signals that are difficult to detect in conventional EEG due to their small source regions from which activity is typically smeared by volume conduction.

A.5 EEG Source Localization

EEG source localization (ESL) is broken into two problems: forward and inverse. Both of these problems must be solved to model EEG sources with dipoles [17, 18]. Identification of the source from signal is the inverse problem. However, the forward problem must be solved before the inverse [17]. The forward problem is the propagation of signals from source to the scalp surface, and its solution is the forward model [19]. Specifically, the head model used and its compartments, surfaces, conductivities and co-registered electrode locations comprise the forward model, also known as the volume conductor [17]. The two most commonly used types of forward models are the simple spherical shell model and the four layered realistic head model derived from patient MRI scans. Shell models may be single layered, modeling only the brain tissue, or they may be overlapping, multilayered with brain, cerebrospinal fluid, skull, and scalp surfaces. Realistic head models
almost always model these four layers and can be broken into two categories: finite and boundary element method (FEM, BEM) models [17]. Unlike the inverse problem, a particular forward model will yield a unique solution. In other words, for a given source within the model a specific potential field at the surface can be calculated. The gain matrix, or lead-field matrix, stores these surfaces potentials that arise from all model dipole activations and is used in the inverse calculation.

The inverse problem is ill-posed. A surface potential does not have a unique source location solution. An infinite number of source configurations can explain a given potential distribution on the surface [17, 18]. The problem is only made solvable by applying mathematical constraints to inverse modeling algorithms. Conceptually speaking, a source space is determined within the model and possible solutions are dipoles constrained to this space. The problem can then be solved with discrete or distributed models. Discrete methods are over-determined [20]. Typically, up to three dipoles are applied to the inverse algorithm to locate sources of the surface potentials in question. As such, there are more electrodes, and data points, than dipole parameters.

The moving and rotating dipole methods are two of the most widely used inverse algorithms. The moving algorithm constrains the dipole in time, allowing it to move freely in space to determine the location, orientation, and strength that best explains the measured EEG data at said instant and then increments in time. In contrast, a dipole is constrained to a location in space, but allowed to change in orientation and strength to best fit the variance in measured data across a time interval, using the rotating algorithm [21].

Since only a few dipoles cannot identify an entire activated source region, it is often advantageous to use distributed source methods over the aforementioned dipolar methods. Moreover, data of lower signal-to-noise ratio can be processed
These methods are underdetermined; there are more dipole parameters than sampling points (i.e. electrodes) [20]. In solving the inverse problem, the number of dipoles is not assumed, and many sources may be active at a given time to explain a particular surface potential. The source space is divided into many points, and each point represents a dipole fixed in location. These dipoles are able to assume any strength but may be constrained in orientation or free to rotate. For example, dipoles may be constrained to the model cortical surface with variable strength and orientation; they may be constrained in a normal orientation to the surface, or they may even be less constrained to anywhere in the cortical layer of the model. Both linear and nonlinear mathematical methods exist to solve the inverse problem with a distributed source space. This research utilized the linear minimum norm estimates (MNE) algorithm since it is most commonly used [17], produces good results when localizing distributed networks of brain activity seen in epileptic discharges, and is robust, allowing for statistical analysis and normalization of the source maps [23, 24, 25, 18]. Moreover, minimum-norm cortical source estimation is robust against error in the skull conductivity parameter of the forward model which is not a well known value [26].

In order to reach a unique solution, this method applies the modeling constraint that neighboring neuronal populations are more likely to synchronize depolarization than non-neighboring ones [27, 18]. A maximum a posteriori (MAP) estimate of the current sources is calculated with the assumptions that the source dipoles are located in the cortex, the amplitudes of the currents have a Gaussian prior distribution with a known source covariance matrix, and the measured data contain additive noise with a Gaussian distribution with a known covariance matrix and is not correlated over time.

In the present research, viable source dipoles were more strictly constrained
to the cortical surface and fixed normal to the surface due to the low number of
channels, N. The MAP current estimate was calculated with the inverse operator

\[ M = R'G^\top(GR^\top G + C)^{-1} \]

where \( G \) is the gain matrix relating the source strengths to measured EEG data,
\( C \) is the data noise-covariance matrix, and \( R' \) is the source covariance matrix [18].
The estimated current amplitude at time \( t \) is given by \( \hat{j}(t) = Mx(t) \), where \( x(t) \) is
a vector containing measured EEG values at time \( t \).

Since the a priori variance of the current is unknown, it can be expressed as
\( R' = R/\lambda^2 \), changing the inverse operator to

\[ M = RG^\top(GRG^\top + \lambda^2 C)^{-1} \]

where the unknown current amplitude is now interpreted in terms of the regular-
ization parameter \( \lambda^2 \). Large current amplitudes and complex estimate patterns
are reflected in small \( \lambda^2 \) while smooth, simpler patterns and smaller amplitude
 correspond to large \( \lambda^2 \). The regularized inverse operator is then determined by
minimizing the cost function

\[ S = \tilde{e}^\top \tilde{e} + \lambda^2 j^\top R^{-1} j \]

where the first term represents the difference between the whitened measured data
and those predicted by the model, and the second term is a weighted-norm of the
current estimate. Finally, the whitened form of the inverse operator is given by

\[ \tilde{M} = R\tilde{G}^\top(\tilde{G}R\tilde{G}^\top + I)^{-1} \]

where \( \tilde{G} = C^{-1/2}G \) is the spatially whitened gain matrix. Expected current values
are then calculated as \( \hat{j}(t) = Mx(t) \), where \( x(t) = C^{-1/2}x(t) \) is the whitened EEG
measurement vector at time t [18, 22].

Here, the identity matrix was used in place of noise covariance as no noise modeling was used. Ideally, segments of recordings that contain only the noise of the sensors are used for noise covariance calculation. This is easier with magnetoencephalography (MEG) as empty room recording is possible, unlike with EEG sensors for which noise depends on the electrode-subject interface. Segments of recordings that do not contain any brain signals of interest are also acceptable, but these can be difficult to define. In each study, baseline recordings were not performed, or defined, for noise covariance calculation. Though, when calculating average event-related potentials in manuscript 2 most sources of noise are eliminated in averaging, so the use of the identity matrix here is of less concern. Without a clear means to distinguish high frequency noise from high frequency epileptic activity it was determined safer to not use any of the recording for noise modeling in manuscript 1. The downside being that an electrode with a higher level of noise could be interpreted as a lot of activity in its brain region.

Inverse modeling algorithms require the solution of the forward problem: the forward model and resulting gain matrix. The choice of head model is important to finding an accurate solution to the inverse problem. Realistic head models offer increased localization accuracy over simple shell models [28], and subject-specific realistic models have been shown to further increase accuracy in identifying epileptogenic zones with biomarker localization in a case study of 152 patients [25]. Other studies have shown that modeling of basal source activity of temporal lobe epilepsy is optimized with the use of realistic forward models [29], and spherical models result in localization error of up to 30 mm in dipole localization. Moreover, spherical models typically result in the mislocalization of known mesial temporal lobe source activity to the frontal lobe [30, 31]. For this reason, subject-specific,
realistic head models were used in the HFA localization in Manuscript 1, as MRI
data for these patients was available. A standard, realistic head model was used
for ERP localization in Manuscript 2.

A.6 Event-Related Potentials

Event-related potentials (ERPs) are small voltages generated in the brain in
response to specific events or stimuli [32]. These EEG signals are time locked to
sensory, motor, or cognitive events. They arise from the summed activity of post-
synaptic potentials produced from pyramidal neurons firing in synchrony while
processing information pertinent to the event [33]. In contrast to raw EEG record-
ings, ERPs are used to isolate potentials related to individual neuronal processes
involved with these events by creating time locked epochs and averaging them.

Because EEG measures the potentials of many simultaneous brain process, the
small response to a single event is not typically seen in the EEG of a single trial.
Assuming the only signal that is time locked to the event is the ERP of interest, the
averaging of many trials, or epochs, will cancel noise and unwanted signals, leav-
ing the ERP. Thus, increasing the number of trials will increase the signal-to-noise
ratio of the average ERP. This noise attenuation with averaging has some limits.
Artifacts or noise of much larger amplitude such as electrooculogram (EOG) ac-
tivity or electromyogram (EMG) activity can still influence the average ERP after
many trials. Epochs containing these artifacts should be removed before averaging.

ERP components are broadly split in two categories. Waveforms that peak
within approximately 100 ms of a stimulus are often referred to as ‘exogenous’ as
they reflect sensory processing of the stimulus. Later components are termed ‘en-
dogenous’ as they reflect the processing of information with respect to the stimulus
[34]. However, this categorization does not always hold true. If the event is initi-
ated by the subject, such as movement, then components before the event reflect
cortical planning. Those that occur during the event and shortly after may reflect processes involved in event execution. Most ERP components are named by the polarity of the scalp potential, N or P, followed by their latency (ms) with respect to stimulus or event. In some cases, the time is replaced by the components’ ordinal position in the ERP. Other components are referred to with acronyms such as contingent negative variation (CNV), error-related negativity (ERN), early left anterior negativity (ELAN), mismatch negativity (MMN), and closure positive shift (CPS).

ERPs have widespread clinical and research uses. Abnormalities in ERP components can help in the diagnosis of dementia [35], Parkinson’s disease [36], multiple sclerosis [37], head injuries [38], stroke [39], obsessive-compulsive disorder [40], and trauma to the visual system [41]. Research in language processing often study ELAN, MMN, N400, and P600 responses [8]. ERPs even have use in brain-machine interface (BMI) applications. The P300 component is consistently elicited in the oddball paradigm regardless of stimulus type. This paradigm is an experimental setup that consists of presenting sequences of repetitive stimuli that are infrequently interrupted by a deviant, or salient, stimulus. The salient, "oddball" stimulus evokes the positive deflection at 300 ms which makes up the P300 response. This consistent response forms the basis for the P300 speller, a BMI device that allows the user to type words by simply staring at characters in a grid. The rows and columns of the grid are randomly flashed, and the flashing of the intended character is the salient stimuli. Thus, the subject can communicate with a P300 response which character to type by staring at it [42].

Here, two types of ERPs with known waveform characteristics and cortical sources are used to compare tEEG and EEG source localization: movement related potentials (MRPs), also known as movement related cortical potentials (MRCPs),
and visual evoked potentials (VEPs). Both are described in detail in manuscript 2.

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APPENDIX B

Conclusion

B.1 Abstract

This appendix serves as the closing section of the thesis. The results of both Manuscripts are discussed as well as the implications of the body of work presented.

B.2 Discussion

The improved SNR and spatial properties of tEEG are significant advantages when performing source localization of scalp potentials. The first manuscript explores the localization of high frequency biomarkers found in patients with epilepsy. These signals are indicative of SOZs and targeted for removal in resective epilepsy surgery. Typical HFOs are not commonly observed in noninvasive EEG recordings, and invasive ECoG is usually required to detect them. However, manuscript 1 provides evidence for the noninvasive detection and localization of narrowband, HFA in the tEEG of patients with epilepsy, and their sources were found almost exclusively in the SOZ.

While improved SNR can help, it is the spatial properties of tEEG that allow for HFA detection on the scalp surface. It is understood that pathological HFOs mainly reflect principal cell action potentials [1]. Synchronization of fast firing within the population of interconnected neurons leads to the formation of high-frequency population spikes, which is extracellularly recorded as an HFO event [1]. This mechanism requires synchronization on a millisecond time scale, which is achieved via fast synaptic transmission between nearby neurons or nonsynaptic mechanisms like gap-junction coupling or ephaptic interactions-a synchronizing mechanism which requires specific geometric organization and tight cellular arrangement. To complicate detection, fast ripples are often observed in frequencies
above 300 Hz, which is approximately the firing limit seen even in epileptic neurons. These signals are produced by closely spaced subpopulations of neurons, each firing at a lower frequency and slightly out of phase such that a net higher frequency is observed [1]. These small, closely spaced sources of high frequency activity are difficult to detect with noninvasive EEG which detects and sums all activity over approximately a 6 sq. cm region of cortex [2], effectively masking these small sources.

However, the TCRE records activity over a smaller cortical region by approximating a local Laplacian, and it spatially samples the same area as a single conventional disc electrode with three sensors, allowing for the amplification of high spatial frequencies on the scalp. It is well documented that the Laplacian emphasizes higher spatial frequencies [3], but the relationship between temporal frequency and the resulting potential distribution spatial frequency on the scalp is less often discussed. In a vacuum, the spatial frequency of a time-series signal will be inversely proportional to its wavelength or directly proportional to its temporal frequency. Given two signals of different temporal frequency that travel at the same velocity, the signal with higher temporal frequency will also have higher spatial frequency. Biological systems of volume conductive and capacitive layers will complicate this relationship, but if we assume that a higher frequency (temporal) cortical source produces a higher spatial frequency of potential distribution on the scalp, then a Laplacian would be better suited for high frequency (temporal) activity detection. Additionally, the increased spatial sampling of the TCRE helps to distinguish the activity of closely spaced sources, whereas conventional discs result in spatial aliasing.

These spatial properties allow for the detection of HFA in scalp tEEG. The major difference between tEEG HFA and previously reported HFOs is that HFA
is much more narrowband in frequency. Figure B.1 is an example of a pathological HFO reported in Roehri et al. [4] (Figure 1B of said article). Note that the circled HFO spans a frequency band of over 100 Hz (approximately 260 to 400 Hz). In contrast, Figure B.2 is an example of an HFA biomarker found in the tEEG of an epilepsy patient. The circled HFA at 320 Hz spans a band of approximately 10 Hz from visual inspection. Other studies have also reported pathological HFOs as more wideband signals [5, 6] when compared to the HFA found in tEEG.

Figure B.1. Spectrogram found in Figure 1B of [4]. Circle indicates fast ripple HFO example. Triangle indicates spike.

These two biomarkers may be different representations of the same underlying physiological processes, but it is difficult, if not impossible, to verify without concurrent recordings of both pathological HFOs (Figure B.1) and tEEG HFA (Figure B.2). Although, much like HFOs, tEEG HFA is indicative of clinical SOZ diagnosis, so it is plausible to believe they have the same underlying physiological sources. In a recent study, pathological HFOs recorded in stereo-EEG (SEEG) of patients with epilepsy were found to resemble the time-frequency characteristics of tEEG HFA [7]. Bipolar recordings of closely spaced contacts recorded HFOs of smaller frequency bandwidth than typically observed. This finding supports the claim that differences of closely spaced electrodes can represent traditional HFOs as more narrowband signals or at least that these two different signals arise from
Figure B.2. Spectrogram of HFA biomarker found in the tEEG of an epilepsy patient. Built from short time Fourier Transform with 1 second Hamming windows of 50% overlap. Activity below 55 Hz and above 500 Hz was filtered, forward and backward for zero phase, with a fifth order Butterworth IIR filter. A 60 Hz notch filter was also applied.

the same underlying sources.

Not only do the spatial properties of tEEG allow for HFA detection but they also produce more focal sources with distributed source modeling, as shown in manuscript 2. Typically, at least 64 channels are needed for adequate localization [8], but the improved focality of tEEG localization may ease this requirement. Higher density montages than the 16- to 19-channel montages used in both manuscripts should be tested. Manuscript 1 provides evidence that with as low as 19 channels the resulting localizations are indicative of the SOZ, but without an exact known source for these biomarkers it is difficult to access the localization precision. The MRP and VEP sources were more focal with tEEG and evidence of improvement. Nevertheless, they reflect regions larger than the known sources
of these signals. Increasing the channel density should improve precision.

Also evident from the VEP results is that montage, specifically head coverage, is important. Mis-localization was due to the sources of the VEPs residing on the edge of the montage. This claim is supported by Song et al. [8] who found that upper head montages, like those used here, were often inadequate when compared to whole head montages and resulted in mis-localization of sources, especially inferior ones. The montage was also not ideal for VEP recording in tEEG. SNR of tEEG is generally higher when compared to conventional EEG [9] but was found lower for most cases of VEP recording in manuscript 2. Three possibilities could explain lower SNR: a decrease in signal detection, increase in noise, or a poor definition of either in the calculation. Time windows for determining signal and noise were empirically determined, so we will rule out the last possibility for this discussion. SNR was lower even in the average tEEG VEP, in which all noise that is not time locked to the stimuli is attenuated. In addition to the visually dampened peaks of the VEP in tEEG, this leads one to believe that the signal was attenuated in the tEEG, indicating the TCRE attenuated the VEP because none were placed in close enough proximity to its source.

One might be tempted to point to the forward model, or lack of a tEEG lead-field matrix, to explain the mis-localization, but that likely isn’t the case because the error occurred with emulated EEG as well. Typically, high resolution EEG techniques such as Laplacian montages aren’t used with dipole source modeling because the lead-field matrix no longer accurately relates the measurement with the dipolar sources. Laplacian montages drastically change the scalp topography [3], but they are also limited by the size and the distance between electrodes. TCREs approximate a more focal Laplacian at the observation site by fitting 3 rings in the space of a single electrode. This configuration results in a scalp topography that
is much more like that of conventional EEG, ignoring magnitude. Albeit activity is more distributed in EEG. Figure B.3a shows the eEEG scalp topography of the representative MRP localization in manuscript 2 (Figure 2.2c), and Figure B.3b is the corresponding tEEG topography of the tEEG localization (Figure 2.2d). While this relationship may not hold true for all sources, the similarity between the two topographies validates the use of a conventional lead-field matrix for this paradigm while also providing a visual representation of the improved spatial resolution of tEEG.

Figure B.3. The average MRP scalp topography for a representative subject recorded with eEEG (a) and tEEG (b).

The development of a tEEG forward model would still add robustness to the procedure and should be explored. Tangential sources are known to contribute less to surface Laplacians than in conventional scalp potentials. Moreover, if sources are not constrained to the cortical surface as done here, then the forward model would not reflect the Laplacian emphasis on superficial sources. While the topographies found here were similar between eEEG and tEEG, other sources may produce
differences due to these properties, potentially causing mis-localization. The most intuitive way to develop a tEEG lead-field matrix would be to calculate matrix values using the nine-point method, as described in Besio et al. [9], on the forward model scalp surface. Then the localization procedure could be performed with the same software only by adding this one extra calculation. For this to work the forward solution scalp surface would require resolution such that the differences between rings approximately 1 mm apart could be distinguished. The FreeSurfer head mask has only 10,000 nodes. If we approximate the average human, upper head as a hemisphere with a 25 cm diameter, then the surface area (neglecting the underside), is approximately 100,000 mm², so the FreeSurfer output is not sufficient for tEEG lead-field matrix calculation in this way. The inverse operator only relies on this matrix from the forward model, so Brainstorm could still be used for localization, but alternate forward modeling methods would be needed. The resulting lead-field could then be imported into Brainstorm and the inverse solution plotted on the present cortex models.

B.3 Implications

The inability to differentiate between physiological, non-pathological HFOs and pathological HFOs is a major obstacle in the analytical use of HFOs for presurgical evaluation in epilepsy [6, 10]. For clarity, the term pathological HFOs (pHFOs) will be used for epilepsy biomarkers and non-pathological HFOs (npHFOs) will be used for normal physiological HFOs. Kudlacek et al. explored a pharmacological approach to solving this problem [11]. Since the rate of pHFOs decreases after treatment with levetiracetam [12] and lacosamide [13], they tested the effects of these two drugs on the rate of hippocampal sharp-wave ripples (SWRs), a npHFO, and found that a single dose of either drug does not reduce their rate [11]. Thus, pharmacological testing stands as viable approach in discriminating
pHFOs from some npHFOs, but SWRs are only one type of npHFO. Extensive testing would have to be done to extend this approach in discriminating pHFOs from all other npHFOs.

For example, event-related augmentation of high-gamma activity at 70-110 Hz in ECoG is used to localize functionally-important regions such as language eloquent areas of the brain [14]. These areas are identified in presurgical evaluation to avoid resection. It is crucial that pHFOs be discriminated from npHFOs during this evaluation process and a pharmacological approach may not always be feasible. Patients may exhibit drug-resistant epilepsy or other npHFOs of interest may be affected by antiepileptic drugs, making discrimination difficult.

This is where tEEG epileptic HFA has an advantage. Event-related augmentation has been shown to reliably track cortical function and is a relatively wider frequency band signal above 50 Hz [15]. These npHFOs span bands of as small as 40 Hz (70 to 110 Hz) and as large as 100 Hz (50 to 150 Hz), and thus, can easily be distinguished from tEEG HFA. Additionally, the TCRE attenuates EMG artifacts [9, 16, 17] that reside in the high gamma frequency range and can hinder analysis of ECoG in presurgical evaluation [14]. Therefore, unlike previously reported pHFOs, the narrowband quality of tEEG HFA offers a unique and simple classification feature for discriminating epilepsy biomarkers from npHFOs.

How these advantages relate to improving the quality of life (QoL) of patients with epilepsy should not be ignored. Burdens of the disorder on patient life satisfaction and QoL among patients and family members are well documented. Personal accounts of patients and their family members often describe challenges that threaten life goals in career and education as well as limitations to self-sufficiency in everyday life such as the ability to drive a car and sleep or shower alone [18, 19]. Other activities such as sports or going to the movies are also lost to some who
actively experience seizures. The fear of an imminent seizure often dictates what these patients can do. In more severe cases, parents of patients are forced to give up dreams for their children and instead hope for nothing more than good health [18]. Even when antiepileptic drugs work, patients can experience mood swings, migraines, dizziness, and nausea as a result. Despite potential negative side effects of treatment, a common theme among personal accounts is the first step to normalcy is a seizure free state.

With respect to epilepsy, life satisfaction and QoL measures aim to quantify these personal accounts. Patients report significantly worse QoL than those without epilepsy, and these measures are even worse for those with active seizures [20, 21]. In 2008, Kobau et al. conducted a study on the HealthStyles survey results to examine satisfaction with life domains in a representative sample of community-dwelling adults with self-reported epilepsy [22]. They found that adults with epilepsy were more likely to experience dissatisfaction with life achievement, education, social interactions, health, and energy level [22]. Additionally, they were more likely to live in households of lower income and less likely to own their homes [22]. Both individual and structural factors act as barriers to explain these results. Unpredictability of seizures and treatments side effects such as lethargy and cognitive impairment compromise motivation and self-efficacy in achieving one’s goals. However, institutional limitations such as job, recreational, and driver’s license restrictions compound these factors along with the stigma that many people with epilepsy endure [22]. As a group, people with epilepsy have more cognitive dysfunction than people without the disorder [23] which can lead to an unfair, negative preconception of individuals who may be more than fit for a task or job.

Mahrer-Imhof et al. conducted a similar study in 2013 which measured subjective QoL of family member/patient pairs [24]. Patient QoL was influenced by
the QoL of their family member, perceived social support within the family, emotional well-being, and lack of concern about seizures. QoL of family members had an increased influence on patient QoL when patients were not worried about their seizures [24]. Perceived social support within the family, patients’ knowledge about medication, and patient activity level were the biggest factors in the family members’ QoL [24]. Moreover, other studies have shown that seizure frequency, form of epilepsy, time since last seizure, and antiepileptic drug side effects were influential variables in health related quality of life (HRQoL) measures in epilepsy patients [25, 26].

For patients with refractory epilepsy, correct identification of seizure generating cortex is crucial for surgical success and subsequent seizure control. Additionally, identifying these regions with more confidence prior to invasive methods will help to reduce patient exposure to risk and resulting stress for them and their families. Mahrer-Imhof et al. found that patients’ knowledge about medication was a major influencing factor on family member QoL [24]. For these patients who have drug resistant epilepsy, it is reasonable to extend this factor as knowledge about treatment in general. Thus, a greater understanding of the patients’ SOZ/IZ and surgical plan could lead to improved family member QoL, which they also found was a main positively influencing factor on patient QoL [24].

Successful seizure control with the lack of negative side effects from antiepileptic drugs would improve patient QoL [25, 26, 24]. However, improved QoL also requires surgeons to avoid resecting functionally important areas of the brain. Currently, event-related augmentation of high-gamma activity at 70-110 Hz on electrocorticography (ECoG) can localize functionally-important regions such as speech-related eloquent areas [14]. These findings are validated by more conventional stimulation techniques which involve stimulating regions of the brain with
intracranial electrodes while the patient answers a question or names an object in a picture. The stimulated site is treated as part of language or speech-related eloquent areas if the patient fails to complete the task or develops a transient sensorimotor symptom such as twitching or tingling in the mouth [14]. Each of these techniques has drawbacks that can negatively affect patient QoL. Aside from the risks of intracranial electrode implantation, stimulation techniques can take up to several hours and may cause stimulation induced seizures. Measurement of high-gamma activity in ECoG is still an invasive procedure, and EMG artifacts can contaminate signals in this frequency range, leading to incorrect identification of functionally important brain regions [14].

The techniques used for tEEG source localization could be extended for non-invasively localizing event-related augmentation of high-gamma activity at 70-110 Hz for eloquent brain tissue identification. We have already shown that tEEG better detects HFA epilepsy biomarkers than other noninvasive measures, and tEEG eliminates both the risks of invasive procedures and stimulation induced seizures. Thus, in addition to improved seizure control by helping to achieve successful surgical outcome, tEEG source localization has potential to help neurologists identify brain regions to be avoided by surgeons to ensure maximal functionality of patients post operation with minimal risk.

Source localization of tEEG could potentially have profound, positive impacts on the QoL of both epilepsy patients who suffer from refractory epilepsy and their family members by minimizing invasive procedures and their risks, helping correct diagnosis of epileptogenic zones, improving patient knowledge of their condition, identifying functionally important areas of the brain, and ultimately leading to a seizure free state with maximal functionality. Consequently, patients would be able to live their lives without the fear of an imminent seizure or the negative side
effects of medications, independently pursuing life goals and happiness.

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APPENDIX C

Higher density VEP recording of a single subject

C.1 Abstract

A 32-channel montage was used to record the VEP in a single subject. Reasoning found in manuscript 2 and appendix B for previous VEP findings is supported by this individual subject. An appropriate montage is paramount for signal detection and localization with tEEG.

C.2 Introduction

A 64-channel amplifier was made available after the writing of manuscript 2 and appendix B of this thesis, lifting the limitation of 16-channel tEEG and eEEG concurrent recording. Using the BrainVision BrainAmp DC amplifier, a 32-channel montage with a high density of electrodes near the primary visual cortex was used to record VEPs in a single subject. The same recording procedure as manuscript 2 was used. Data was sampled at 2500 Hz in the Brainvision Recorder software and was filtered from 0.0159 to 1,000 Hz by the amplifier. Using the processing methods described in that manuscript, this recording was done to evaluate the reasoning for previous results: a suboptimal montage with inadequate head coverage for VEP recording was used. The present montage produces substantially better results in tEEG VEP SNR, resolution, and localization accuracy.

C.3 Results

The SNR of the VEP recorded with tEEG was significantly higher (t test, p <0.05, not shown) than that of eEEG for all N-trials (Figure C.1a) when taking advantage of the current montage. However, when only utilizing the posterior channels in the montage from manuscript 2 (Figure C.1b), the SNR was greater in eEEG for N-trials >60. Average VEPs recorded with eEEG and tEEG are shown.
in Figure C.2a and C.2b respectively. For both, the highest amplitude VEP was recorded in channels POz and PO4. Neither of these were used in the previous recordings. Localization of the tEEG VEP (Figure C.2d) appeared much more focal than that of eEEG, and VEPs were correctly localized to the primary visual cortex in both measurements.

Figure C.1. Signal-to-noise ratio of VEP recorded with tEEG (green) and eEEG (blue) as a function of number of trials. SNR shown in panel (a) was calculated as described in manuscript 2 except that the highest SNR between all channels was used instead of a subset around the occipital lobe. SNR shown in panel (b) was calculated with only the five channels used in manuscript 2. SNR of tEEG is significantly different than that of eEEG for all N-trials in both panels (t test, p <0.05 not shown).

C.4 Discussion

This single subject VEP recording was performed to validate the reasoning for prior results. The 32-channel montage produced great improvements in localization and resolution. The VEP was localized to the primary visual cortex as expected in both eEEG and tEEG, and the gain in source resolution produced in tEEG appears to be much greater than that from the 16-channel montage. In fact, if an approximate source location is known before recording, then a 32-channel montage with a focused, higher density of electrodes near the source should be used in future
Figure C.2. The average VEP recorded with eEEG (a) and tEEG (b). MNE localization (occipital lobe) of the peak approximately 150 ms post checkerboard reversal found in eEEG (c) and tEEG (d).
localization studies with the TCRE. This setup allows for precise localization and full head coverage with as little as 32 channels.

Again, the conventional lead-field matrix is used for localization with both eEEG and tEEG. The scalp topography at approximately 150 ms (time of localization in Figure C.2) is shown in Figure C.3a and Figure C.3b respectively. Notwithstanding magnitude, the similarities between the two topographies validate the use of this forward model, as the EEG lead-field matrix appears to relate dipole sources to tEEG measurements sufficiently for localization. This result doesn’t change the fact that a tEEG lead-field matrix would improve results, but it would come with the increased computational cost required for a forward model with sufficient resolution to determine differences between TCRE rings.

Worth noting is the difference in tEEG magnitude when compared to manuscript 2. Unlike in the manuscript, the tEEG data was divided by the pre-amplifier gain of 187.5 to approximate the surface Laplacian magnitude. This
division of the gain does not alter SNR or localization precision, but it drove the magnitude of signals down low enough (approximately $\pm 0.2 \mu V$) such that the Brainstorm scale bar was set to its minimum of $0 \mu V$. Gain cancellation was performed in manuscript 1 but not manuscript 2.

Most notably of these results is the influence of montage on tEEG SNR. Previously, for most N-trials the VEP SNR was higher in eEEG with the 16-channel montage in manuscript 2. However, in its calculation as the highest SNR found in each of 32 channels here (Figure C.1a), tEEG produced significantly higher SNR for all N-trials. With this same recording but only using the same five channels as in manuscript 2 (Figure C.1b), the eEEG SNR remained unchanged, but the tEEG SNR was decreased and found to be significantly lower than that of eEEG for N-trials $>60$. Thus, it is confirmed that the montage choice in manuscript 2 was cause for the atypically low tEEG SNR of VEPs. Although limited to one subject, these results also support the hypothesis that a lower of number of trials are needed in tEEG for a desired SNR. For example, if one would require an SNR of 10 dB, then tEEG may need as little as 40 trials of an ERP, whereas EEG could require several hundred.

Because conventional EEG electrodes record the summed activity over a large brain area, they show asymptotic improvement in precision with respect to localization as number of channels is increased. Increasing electrode density does not seem to greatly improve resolution after 64 channels [1] since these sensors are recording much of the same information. The unchanged eEEG SNR after removing additional channels (Figure C.1b) indicates this redundancy. Unlike conventional EEG electrodes, TCREs have sufficient spatial resolution to take advantage of higher density montages. This advantage comes at the price of montage choice. Greater care is needed in deciding electrode locations in tEEG, but if done correctly it
produces improved signal detection and localization precision.

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