8-13-2024 9:00 AM

The Effect of High-frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges

Ahdyie Ahmadi,

Supervisor: Martinez-Trujillo, Julio, *The University of Western Ontario*
Co-Supervisor: Suller Marti, Ana, *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

Abstract

More than 15 million patients with epilepsy suffer from drug-resistant epilepsy (DRE). In these cases, a successful surgical outcome entails the removal of the seizure onset zone (SOZ), the brain region(s) responsible for seizure initiation. In this regard, finding robust biomarkers of epileptogenicity will help clinicians to accurately localize the SOZ. In focal epilepsies, interictal epileptiform discharges (IEDs) are paroxysmal events observed in both epileptogenic and non-epileptogenic zones.

To identify the SOZ, extraoperative cortical stimulation (CS) is used during phase II of the presurgical investigation. We evaluated the impact of CS on IEDs to find biomarkers of epileptogenicity to accurately find SOZ.

In this study, intracranial signals were recorded from thirty DRE patients (seizure-free post-surgery) implanted with depth electrodes (stereo-electroencephalography) for presurgical evaluation. Bipolar and high frequency (50 Hz) CS was performed with a pulse width of 300 μs and current spanning 1–6 mA. Following preprocessing, IEDs were automatically detected pre- and post-stimulation, and their normalized absolute changes were compared between SOZ and non-SOZ.

Our findings reveal a significant increase in IED numbers following CS over SOZ compared to non-SOZ stimulation (Mann-Whitney U test, $p < 0.001$). Furthermore, this increase extended beyond the stimulated site, indicating a broader effect of stimulation on the SOZ. These results feature the potential of tracking post-stimulation changes in IEDs' characteristics as a quantitative method for SOZ identification, enhancing localizing the SOZ with greater precision.

Keywords: Interictal Epileptiform Discharges, Stereoelectroencephalography, Seizure Onset Zone, Cortical Stimulation

Summary for Lay Audience

Millions of people worldwide suffer from epilepsy, and some have a severe form that does not respond well to medication. When surgery becomes an option, clinicians need to find the exact spot in the brain where seizures start to remove them.

In our study, we looked at how stimulating certain parts of the brain helps clinicians find this spot. We studied thirty patients who did not become seizure-free with medication. We used a special type of brain stimulation and applied mild electric pulses to specific brain regions. Then, we looked at the electrical activity in different areas before and after the pulses.

We found that after stimulating the spot where seizures start, there was a clear increase in abnormal brain activity. This increase was not just in the stimulated area but spread out, showing that stimulation could help clinicians find the right spot to be resected more accurately.

By understanding these changes, clinicians can improve their ability to treat epilepsy with surgery, giving patients better chances for a seizure-free life.

Co-Authorship Statement

Credit to Dr. Greydon Gilmore for Figure 6.

Credit to Dr. Mohamad Abbass for Figure 8.

Acknowledgments

I would like to express my gratitude to my supervisors Dr. Julio Martinez Trujillo and Dr. Ana Suller Marti, for their invaluable guidance throughout my research journey. Their knowledge, insightful feedback, and constant encouragement have been instrumental in shaping my research and ensuring its quality. I would like to thank my advisory committee members, Dr. Ali Kan, Dr. Mark Daley, Dr. Giovanni Pellegrino, and Dr. Stefan Kohler for their insights into my project. I am also deeply thankful to my examiners, Dr. Jonathan Lau, Dr. Giovanni Pellegrino, and Dr. Maryam Nouri for taking the time to review my thesis.

I would like to acknowledge my clinical mentors Dr. Greydon Gilmore and Dr. Hellen Kreinter and lab members especially Dr. Ben Corrigan, Dr. Mohamad Abbass, and Dr. Juan Pimiento for their collaboration and countless hours of meaningful discussions. Their assistance has significantly contributed to the success of this project.

Lastly, I express my deepest appreciation to my family and friends for their unwavering encouragement and love. Their constant belief in me has been a tremendous source of motivation and strength, providing the emotional support needed to overcome challenges and persevere.

Table of Contents

List of Figures

List of Tables

Chapter 1

1 Introduction

1.1 Epilepsy

Epilepsy, often referred to as a seizure disorder, is a chronic neurological condition characterized by recurring epileptic seizures (R. S. Fisher et al., 2014). It affects approximately 50 million individuals worldwide, making it one of the most prevalent neurological disorders globally, impacting people of all ages. The International Bureau for Epilepsy and the International League Against Epilepsy have defined the terms epilepsy and epileptic seizure. An epileptic seizure is a sudden occurrence of symptoms resulting from synchronous neuronal discharge or abnormal excessive activity within the brain(Kassie J. Bollig, 2018). Epilepsy, on the other hand, is marked by a persistent predisposition to experience epileptic seizures, along with the far-reaching psychological, neurobiological, cognitive, and developmental impacts associated with this condition. Diagnosis of epilepsy necessitates the incidence of at least one epileptic seizure(R. S. Fisher et al., 2005).

1.2 Seizure types

Epileptic seizures are broadly categorized as either generalized or focal. Generalized seizures involve abnormal neuronal activity that affects both hemispheres of the brain simultaneously, leading to widespread symptoms. In contrast, focal seizures originate from specific regions of the brain, implying localized abnormalities in neuronal function.

Focal seizures can vary in severity depending on the extent to which the abnormal electrical discharges spread within the brain. They may cause mild or severe symptoms, ranging from subtle changes in sensation or perception to more pronounced motor or cognitive impairments. It is noteworthy that generalized seizures can sometimes originate as focal seizures, beginning in a localized area of the brain before spreading to involve both hemispheres. This progression underscores the dynamic nature of seizure activity and its potential to evolve into broader manifestations affecting the entire brain (Lopes et al., 2020).

1.3 Drug-resistant epilepsy

Approximately 70% of individuals diagnosed with epilepsy could become seizure-free with the proper use of antiseizure medicines (ASM). However, around 15 million epilepsy patients still experience the persistence of seizures despite at least two syndrome-adapted antiseizure drugs used at effective daily doses. This condition is defined as drug-resistant epilepsy (DRE) by the International League Against Epilepsy(Guery & Rheims, 2021).

All patients diagnosed with drug-resistant epilepsy must undergo evaluation in an epilepsy center. This evaluation is particularly important for discussing the potential eligibility and suitability for non-pharmacological therapies. Epilepsy centers offer specialized expertise and resources necessary for comprehensively assessing each patient's condition and tailoring treatment plans to their individual needs. By exploring non-pharmacological therapies such as epilepsy surgery, deep brain stimulation (DBS), responsive neurostimulation (RNS), or vagus nerve stimulation (VNS),

patients with DRE can potentially achieve better seizure control. Lastly, Considering the profound impact of DRE on social integration and psychological well-being, it is essential to implement comprehensive care adaptations aimed at enhancing patients' quality of life (Li et al., 2021; Marti et al., 2022; Samanta, 2022).

1.4 Seizure Onset Zone

Drug-resistant epilepsy patients who have focal seizures can be candidates for epilepsy surgery. However, one of the most important factors for a successful surgical outcome (complete seizure abolition) is the removal (or disconnection) of the seizure onset zone (SOZ), which is the specific brain region(s) responsible for seizure initiation(Epileptogenic Zone, n.d.). Therefore, the SOZ should be localized accurately to allow clinicians to proceed with subsequent surgical resection (Jobst et al., 2010; Marti et al., 2022).

1.5 Non-invasive presurgical evaluation

To find the SOZ, patients undergo a thorough epilepsy assessment (phase I) comprising non-invasive investigations. These include functional imaging (single-photon emission computed tomography co-registered to MRI, positron emission tomography), neurophysiological imaging techniques (magnetoencephalography, EEG-fMRI, high-density EEG, monitoring pathological HFOs, magnetic and electrical source imaging,), structural MRI, (ultra-high-field imaging at 7 Tesla, advanced protocols for imaging acquisition and image processing techniques), and fMRI. Recent developments in the abovementioned techniques have significantly enhanced non-invasive presurgical evaluation and in many cases can provide clinicians with sufficient information to estimate the epileptogenic zone (EZ). It is worth mentioning that there is no direct preoperative measurement of the EZ: Its delineation is a purely conceptual exercise incorporating data derived from multiple tests and various components of a presurgical evaluation (Baumgartner et al., 2019; Rosenow & Lüders, 2001).

1.6 Intracranial Monitoring

If the obtained information from the presurgical evaluation (Phase I) is inadequate to localize the SOZ, patients may undergo invasive electrode implantation for intracranial monitoring of electrical activity (Gonzalez-Martinez et al., 2013). This intracranial recording is done either through electrocorticography (ECoG) which involves placing electrodes on the surface of the brain (subdural grid) or via stereoelectroencephalography (SEEG) which involves implanting multiple depth electrodes into the brain, typically guided by MRI or CT images. SEEG can provide extensive coverage of both hemispheres, enables targeting of deep brain structures, is comparatively less invasive, and is currently preferred over subdural grids(Smith et al., 2022).

1.7 Interictal Epileptiform Discharges

In the intracranial recordings, there are frequently abundant sporadic electrophysiological phenomena (pathological patterns of epileptic activity) known as Interictal Epileptiform Discharges (IEDs) which are biomarkers for epilepsy. Spike waves of IEDs, consisting of a negative polarity deflection and a sharp peak, which is usually followed by a slow wave, stand out from the background activity and have a duration of 10 to 100 ms(Brown et al., 2007). One of the potential explanations for the origin of spike waves is an increase in excitatory interactions within glutamatergic neuronal networks(De Curtis et al., 2012). Some studies suggest that a neuronal discharge is initiated by bursting pyramidal cells and possibly terminated by the activity of inhibitory interneurons; others, however, propose more complex interactions within various neuronal types(Hofer et al., 2022; Truccolo et al., 2011).

1.8 Stimulation to probe the epileptic brain.

Stimulating neural tissue through electrical pulses can induce responses that not only persist but also propagate beyond initial stimulation sites, often resulting in significant amplifications.

Seizures are a prime example of this excitability principle. Electrical cortical stimulation techniques have been used in DRE treatment for almost a century and have recently undergone a resurgence due to their remarkable potential to explore, activate, and suppress brain activity(Frauscher et al., 2023). Evidence indicates that stimulation improves both diagnosis assessment and therapeutic outcomes for DRE individuals; nevertheless, cortical stimulation is not performed in all epilepsy centers across the world. Epilepsy disorder is marked by intricate dynamics of the brain states; thus, to achieve optimal responses to cortical stimulation in DRE epilepsy, a precise selection of implantation targets and stimulation parameters are required. In other words, depending on the chosen stimulation parameters, electrical stimulation is delivered to the epileptic brain for seizure localization and therapeutic purposes (Frauscher et al., 2023).

1.8.1 Exploring excitability through stimulation

Cortical stimulation activates neuronal tissues and monitoring the brain's responses to these perturbations sheds light on pathological connectivity and cortical excitability within the epileptic brain network. An example of that is single-pulse electrical stimulation (SPES) which involves delivering brief pulses of current to targeted regions across the brain. The resulting neural response, commonly referred to as cortico-cortical evoked potential, is captured to delineate the effective connectivity over the response and stimulus sites (Frauscher et al., 2023a; Matsumoto et al., 2004, 2017).

While cortico-cortical evoked potentials were primarily studied to delineate physiological connections within functionalized circuits, the technique quickly transitioned to epilepsy research to define areas of heightened cortical excitability and delineate epileptogenic subnetwork nodes(Matsumoto et al., 2007). However, the interpretation of the results is center-dependent, and it is not commonly used in epilepsy centers(Frauscher et al., 2023a).

1.8.2. Stimulation to induce patients' typical electro-clinical seizures

Intracortical stimulation serves dual purposes: seizure onset zone identification and eloquent cortex mapping. While cortical stimulation is widely applied to map the functional cortex, its application in identifying the seizure-onset zone is less established, despite being initially introduced in the twentieth century (Poerster & Penfield, 1930)).

A 2016 review conducted by Kovac et al., indicated that evidence concerning the advantage of inducing patient-specific electro-clinical seizures for predicting postsurgical outcomes remained inconclusive. Two recent multisite studies have provided insight into this question; In these studies, it was shown that stimulating patient-typical electro-clinical seizures with SEEG serves as a valuable method for identifying the epileptogenic zone and predicting surgical outcomes (Frauscher et al., 2023; Trebuchon et al., 2021; Cuello Oderiz et al., 2019). In their 2019 study, Cuello-Oderiz et al. studied 103 DRE patients who underwent stereo-electroencephalography with at least a session of electrical stimulation followed by open resection surgery. The electro-clinical seizures were induced in 57% of the patients. The incidence of patient-typical electroclinical seizures triggered by electrical stimulation was higher in the cohort with favorable outcomes (Engel class I) compared to the cohort with less favorable outcomes (Engel class II-IV). Additionally, patients with favorable surgical outcomes had a larger proportion of resected channels covering the seizure onset zone compared to those with poorer outcomes. Notably, the findings showed no difference compared to observations with spontaneous seizures, indicating that spontaneous seizures and patient-typical seizures triggered by stimulation offer comparable insights into the seizure-onset zone (Frauscher et al., 2023a). 346 patients underwent a thorough investigation in Trébuchon et al. 2020 study and seizures were induced through stimulation in 75.3% of cases. Their findings also indicated that patient-specific seizures induced by 1-Hz stimulation were predictive of positive surgical outcomes, with a subsequent 44% chance of recurring disabling seizures during the final follow-up assessment. Trebuchon et al, in their 2020 multivariate study, found that the occurrence of stimulation-induced patient-specific ictal events offered additional insights beyond conventional factors for predicting surgical outcomes, including MRI results, type II focal cortical dysplasia, and the presence of a tumor. Previous studies indicated that seizures were more easily triggered using 50 Hz compared to 1 Hz stimulation (Munari et al.,

1993a), often resulting in seizure onsets detectable following stimulation artifacts. Recent research reported that, out of all studied variables, the stimulation frequency (50 Hz versus 1 Hz: 54.9% versus 18.2%) and a longer interval since the last ictal event (over 24 hours) were significantly correlated with an increased probability of inducing patient-specific electro-clinical seizures(Cuello Oderiz et al., 2019). Trébuchon et al. (2020) arrived at a parallel conclusion, noting that only 6.6% of inductions occurred only with low-frequency stimulation, while 40.8% occurred with high-frequency stimulation, and 27.9% were induced using both frequencies (Frauscher et al., 2023a). Furthermore, their findings indicated that inducing patient-specific seizures using 1 Hz stimulation served as a significant positive predictor of favorable seizure outcomes following epilepsy surgery. This discovery highlights the potential for specific stimulation parameters to enhance surgical prognoses. A significant clinical benefit of inducing patient-typical seizures is the capability to monitor the progression of signs and symptoms, along with the electro-clinical correlation, within a controlled setting (Trebuchon et al., 2021). Concerning underlying pathologies, existing studies indicate that stimulation-induced seizures are more prevalent in specific conditions. This increased susceptibility may be attributed to the abnormal cortical architecture and heightened excitability characteristic of such pathologies (for example focal cortical dysplasia type 2.). Understanding these differences is crucial for tailoring stimulation protocols and improving the accuracy of interventions in patients with varying neurological conditions(Chassoux et al., 2000). Furthermore, different parameters of stimulation to trigger patient-typical electroclinical seizures differ across institutions (Trébuchon & Chauvel, 2016), with some employing low-frequency stimulation, others high-frequency, and some utilizing a combination of both methods. The initial intensities are chosen according to several factors, including pathology, electrode type, stimulation type, pulse duration, anatomical structure under study (lower intensities required for dysplastic tissue, the sensorimotor cortex, mesio-temporal lobes), ASM dosage, the time elapsed since the last ictal event, and history of seizure generalization (Prime et al., 2018). To prevent tissue damage, it is recommended not to exceed a charge density of approximately 57 $\mu C/cm^2$ and to minimize the potential neuronal injury (Gordon a-c et al., 1990). Because charge density relies not only on pulse width and output current but on macroelectrode surface area as well, the intensity of stimulation varies between subdural contacts and SEEG (Frauscher et al., 2023a).

Patients generally exhibit good tolerance to the side effects of stimulation aimed at inducing patient-specific electro-clinical seizures especially when they receive thorough explanations and procedures follow established protocols. False positive responses, which involve stimulating non-habitual electro-clinical seizures, appear to be infrequent via stereo electroencephalography, documented at 1.5% with low-frequency stimulation and approximately 8% for high-frequencies. Contrary to its usefulness, supplementary research is required to definitively determine the additional significance of stimulating patients' seizures as part of the array of biomarkers for predicting surgical outcomes (Cuello Oderiz et al., 2019; Frauscher et al., 2023).

1.8.3. Stimulation to stop interictal activity and seizures.

A substantial body of research on stimulation has aimed at decreasing seizure frequency in patients (Simpson et al., 2022; Ryvlin et al., 2021). Supervised and well-planned clinical trials performed in a controlled setting, along with registry data, validate longstanding clinical effectiveness of different stimulation techniques (R. Fisher et al., 2010; Nair et al., 2020; Englot et al., 2016; Salanova et al., 2021; Morrell, 2011). In contrast to antiepileptic drugs, the precise configuration of electrode contacts relative to brain structures and consideration of specific stimulation parameters are of paramount importance (Frauscher et al., 2023a).

Despite varying parameters and targets among different stimulation approaches, their overall long-term efficacy remains similar. Most brain stimulation techniques achieve a median seizure reduction of approximately 50-70% after 3-5 years. Furthermore, evidence indicates that efficacy improves over an extended period, implying that some mechanisms of action may work at a slower pace. In certain instances, brain connectivity and interictal epileptiform activity exhibit noticeable changes in response to stimulation over periods of months to years, though faster reductions have also been observed(Chiang et al., 2021, Lundstrom et al., 2019, Arcot Desai et al., 2019). Typically, the main outcomes have been a decrease in the frequency of seizures rather than their immediate cessation (Frauscher et al., 2023a).

The evidence supporting the immediate cessation of seizures through stimulation in focal epilepsies is inadequate, suggesting it may not be the most effective long-term therapeutic approach. Conclusive evidence shows that high-frequency stimulation can terminate after-discharges (consisting of repetitive epileptiform potentials, rhythmic waves, or both following a precipitating stimulus) and focal seizures. A 1999 study conducted by Lesser et al. utilized the opportunity of electrical stimulation while performing functional cortex mapping to explore the effectiveness of stimulation in terminating evoked after-discharges and seizures. Their findings revealed that high-frequency electrical stimulation (50 Hz, charge-balanced square wave, 300 μs pulse width) effectively suppressed induced after-discharges. Following this, NeuroPace, Inc. sponsored a multicenter trial that further explored this promising finding using a bedside external responsive neurostimulation system which ultimately led to the development of a fully implantable RNS system (Frauscher et al., 2023a).

Nevertheless, terminating spontaneous, habitual seizures, has been challenging in ambulatory patients unlike the seizures induced by stimulation during brain functional mapping. While clinicians using the NeuroPace RNS device rarely observe seizures being directly stopped by stimulation, they often note significant clinical improvements and reduction in seizure frequency, with the device delivering hundreds of stimulations daily(Frauscher et al., 2023a; Nair et al., 2020).

Although there are documented cases where RNS successfully aborts spontaneous seizures in humans, such occurrences are relatively rare. This is primarily due to the intricate epileptic brain organization (Frauscher et al., 2023a; Stead et al., 2010). when a seizure is detectable on electrodes, it has already recruited extensive neural networks, making it challenging to control with electrical stimulation. By the time acute cessation occurs, high-frequency stimulation may lead to functional lesions through depolarization blocking, suppressing the activity of neurons in the nearby area. In general, the process of seizure termination remains a crucial topic in epileptology. Since there is no reported research on the direct comparison between close-loop ongoing responsive cortical stimulation and open-loop stimulation, distinct and potentially supplementary mechanisms through which they affect cortical physiology are still unexplored. Lastly, during an ongoing seizure, different responses to stimulation are expected within a seizure network. Therefore, underlying mechanisms associated with seizure onset, spread, and termination and properties of

stimulation targets are the primary indicator factors for chronically decreasing seizure frequency or terminating them with stimulation (Frauscher et al., 2023a; Lado & Moshé, 2008; Jiruska et al., 2013; Kramer et al., 2012; Timofeev & Steriade, 2004; Russo et al., 2023).

1.8.4. Stimulation parameters

It is worth noting that neurons, the brain's fundamental computational units, primarily communicate through electrical signals (in addition to chemical signals such as hormones and local extracellular signaling) and these electrical oscillations play a crucial role in neural interactions. Therefore, understanding the electrical brain functions from different perspectives can be effectively approached within the context of dynamical systems, given their ability to model complex, nonlinear interactions and temporal dynamics. However, it is important to recognize that there are various other methods and perspectives for studying neural networks (Frauscher et al., 2023a).

Pertinent brain states in epilepsy can be classified as including ictal and interictal phases. The brain may fluctuate between these two conditions with varying stability degrees, potentially leading to seizure generation as it nears tipping points (A tipping point is a critical threshold at which a small change or perturbation can lead to a significant shift from one stable state to another) (Frauscher et al., 2023a; Maturana et al., 2020)

The stability of these states may decrease or increase with the application of external electrical impulses. For instance, for therapeutic purposes, external electrical stimulation is delivered to enhance the interictal state's stability. Evidence indicates that interictal epileptiform discharges that is said to act as endogenous electrical impulses, may either help maintain the interictal state or increase the likelihood of transitioning to an ictal state (Chvojka et al., 2021; Frauscher et al., 2023a). To put it another way, interictal discharges within a neural subnetwork can serve as external perturbations, shifting the system into another stable state, such as ictal, as it nears a tipping point. The brain, conceptualized as a dynamical network undergoing transitions from ictal to interictal states through phase transitions, presents a sample of phenomenological models

(Frauscher et al., 2023a). In this context, a phase transition refers to a change in the state of the system (from interictal to ictal) that occurs when a critical threshold is crossed. However, the concept of critical slowing down—a phenomenon where a system's recovery time from perturbations increases as it approaches a critical point— a hallmark of such systems, remains controversial in the context of epilepsy (Frauscher et al., 2023a; Wilkat et al., 2019).

Seizure dynamics are inherently intricate (Saggio et al., 2020). Sixteen unique patterns of dynamics, referred to as dynamotypes, have been identified using amplitudes of EEG and the temporal gaps between epileptiform discharges observed at the initiation and cessation of seizures. Even within individual patients, these dynamics can vary between different ictal states. Moreover, patterns of seizure propagation and their duration can differ independently(Frauscher et al., 2023a; Schroeder et al., 2022). According to these differing dynamics of the brain, it is also expected that the accuracy of EEG biomarkers of epileptogenicity may vary as well(G. Smith & Stacey, 2021). Contrary to the mentioned differences, there are yet sufficient similarities that enable the effective categorization of extensive collections of SEEG ictal records across different patients(Arcot Desai et al., 2019).

Considering the intricacies of brain dynamics, it is unsurprising that, depending on the brain state and patient, a given set of stimulation parameters could yield various effects. For instance, responsive neurostimulation at 100 Hz proved more effective when the brain was in low-risk states for the occurrence of a seizure, whereas 200 Hz had higher efficacy during high-risk states(Chiang et al., 2021). Generally, the frequency at which stimulation is delivered is typically seen as a key parameter, with frequencies of 100 Hz or higher being commonly used in RNS. Nevertheless, RNS at low-frequency (7 Hz) can result in significant outcomes relative to 100-200 Hz stimulation in individual patients (Frauscher et al., 2023a; Alcala-Zermeno et al., 2023). The mention of low-frequency RNS (7 Hz) yielding significant outcomes in some patients underscores the variability in patient responses to stimulation. This variability highlights the need for personalized approaches in neuromodulation. In a rat limbic epilepsy model, using stimulation to terminate ictal activities is associated with improved effectiveness when the stimulation frequency aligned with the natural frequency observed during seizure cessation, ranging between 7 and 300 Hz. These findings are verified by computational studies, which suggest that the frequency of stimulation required to stop

seizures depends on the underlying dynamics. Specifically, slower ictal dynamics necessitate lower stimulation frequencies to achieve efficacy(Sobayo & Mogul, 2016; Ersoz et al., 2020;Frauscher et al., 2023a)

Certainly, while brain state dynamics and stimulation parameters can influence outcomes, there are instances where even basic, standardized approaches prove equally effective.

1.8.5 Extraoperative Electrical Cortical Stimulation

Intracortical stimulation is primarily used to map the functional cortex, including language, motor, sensory, and visual areas to prevent or reduce the potential risk of any unintended neurological damage(Marti et al., 2022). This technique also offers the opportunity to delineate seizure networks and cortical connectivity. CS provides a valuable opportunity to investigate inter-individual differences in the cortical representation of various brain functions(Munari et al., 1993b). It can be applied in a temporally and spatially targeted way, through implanted depth electrodes used to record neural activity termed extraoperative cortical stimulation, or in the operation room, before resection, referred to as intra-operative stimulation (Ezzyat & Suthana, n.d.). Both methodologies have their constraints, however, extraoperative CS presents distinct advantages over intraoperative ones. Outside the operating room, there are fewer time limitations, facilitating the possibility of repeating or meticulously analyzing CS procedures multiple times. Conversely, intraoperative CS is typically confined to a small region that can be stimulated during surgery, resulting in a less reliable assessment of a broader neuronal network's functionality. Additionally, patients generally tolerate extraoperative CS better than intraoperative stimulation during awake craniotomy. Enhanced tolerance and cooperation often yield superior stimulation outcomes in most cases.

1.8.6 Outlook

Electrical stimulation is currently used for both the treatment and diagnosis of epilepsy, yet it is not as straightforward as prescribing an ASM with an appropriate dosage. It is important to

acknowledge the intricate dynamical complexity of the brain, which can often be overlooked in these considerations(Simpson et al., 2022).

Electrical stimulation can trigger and suppress seizures. The existing data have not definitively established significant differences in long-term effectiveness between closed versus open-loop and low versus high-frequency stimulations, despite the prevailing belief that high-frequency and closed-loop methods may provide better results. On the contrary, evidence indicates that, for probing the epileptic brain, low-frequency stimulation can be more efficient. While high-frequency stimulation more readily evokes seizures, low-frequency stimulation leads to improved prognostication of surgical outcomes(Trébuchon & Chauvel, 2016; Cuello Oderiz et al., 2019). Brain states are dynamic (constantly in fluctuation), and the application of cortical stimulation is expected to manifest various effects across time and space (Frauscher et al., 2023a).

1.9 Epilepsy biomarkers

A biomarker is characterized as an objectively measurable feature of a pathological or normal biological process. Identifying and validating biomarkers for epileptogenicity (the potential of brain tissue to generate seizures), epileptogenesis (the process of developing epilepsy after a brain insult), and ictogenesis (the mechanisms leading to the initiation of seizures) could potentially reveal the presence and severity of seizure-prone tissue, predict the onset of epilepsy, monitor progression once the condition is established, and help determination of pharmacoresistance (Engel et al., 2013). Research aimed at identifying reliable biomarkers such as interictal epileptiform discharges and high-frequency oscillations may also uncover underlying mechanisms that could serve as therapeutic targets for the development of new antiseizure and antiepileptogenic compounds. Epileptogenic abnormalities may also fluctuate over time, therefore, the likelihood of a seizure occurrence may be decreased or increased depending on different physiological factors. Another consideration is whether some biomarkers can be applied to all epilepsies while others may be specific to particular syndromes. Given that biomarkers for epileptogenesis may be confined to specific time points (such as EEG during the acute phase after a traumatic injury), it is crucial to precisely define the syndrome,

the biomarker, and the appropriate time window. SEEG is the gold standard method for the presurgical evaluation of focal drug-resistant epilepsy(Marti et al., 2022). However, predicting surgical outcomes on an individual level is challenging. For this purpose, a quantified estimation of the most epileptogenic regions by identifying relevant biomarkers can be proposed (Makhalova et al., 2023). In patients undergoing evaluation for epilepsy, electrophysiological recordings are performed to detect seizures and verify the presence of epilepsy. Intracranial EEG recordings are used to identify the brain regions where seizures originate and in surgical interventions help in planning the resection areas. Since seizures can occur infrequently and are unpredictable, ictal recordings may not be ideal in terms of cost, time, and risk. This is particularly true when evaluating the potential of different anti-epileptogenic interventions, assessing the effect of current or new ASM, or for extended intracerebral electrode investigations. Therefore, there is a necessity for the identification and validation of alternative electrophysiological epilepsy biomarkers that could facilitate treatment, diagnosis, cure, and prevention of the condition. Intracranial recordings from the epileptic brain typically contain other electrophysiological disturbances that occur more often than seizures, such as interictal epileptiform discharges which can accelerate and facilitate the process of identifying the SOZ(Frauscher et al., 2023a; Staba et al., 2014).

1.10 The effect of stimulation on IEDs

To find SOZ biomarkers, some studies have reported the effects of intraoperative cortical stimulation on IEDs detected in intracranial recordings using subdural grids. Nakatani et al. found that high-frequency stimulation of SOZ decreases the amplitude of spikes and the number of IEDs(Nakatani et al., 2020). Similar results were documented by Kinoshita et al.(Kinoshita et al., 2004, 2005). These studies provide valuable insights into the clinical utility of cortical stimulation for managing epilepsy through neuromodulation techniques. Nevertheless, in certain situations, particularly while using SEEG, stimulation techniques have been utilized to trigger seizures. The reciprocal impacts of cortical stimulation can be elucidated by considering the degree to which GABA-mediated modulation is involved. Generally, interneurons release GABA, which typically

inhibits other neurons, helping to control excessive brain activity. However, when many interneurons fire simultaneously, they can create synchronized inhibitory signals across a large network of neurons. After a strong inhibitory signal, the neurons can exhibit a rebound excitation. When the inhibitory effect wears off, the neurons might fire together in a synchronized manner, which can trigger a seizure (Neumann et al., n.d.; van Klink et al., 2016).

In this regard, little is known about how characteristics of IEDs change in response to 50 Hz cortical stimulation using SEEG and whether analysis of the changes in detected IEDs before and after stimulation could provide insights into localizing seizure onset zones.

1.11 Current study

Despite the use of intracranial recordings and other qualitative analyses to define the SOZ, surgical success rates still vary widely between 30% and 70%. Furthermore, the effectiveness of predefined short-term diagnostic biomarkers in predicting outcomes over the long term, their additional value compared to current SEEG recordings, and the potential for biomarker-guided interventions to achieve seizure freedom remains uncertain (R. J. Smith et al., 2022, Guo et al., 2020). Therefore, developing quantitative assessments for identifying the SOZ is critical for improving outcomes.

In this study, we will investigate spike activity at both stimulated and non-stimulated contacts to determine whether stimulation-induced interictal epileptiform discharges can provide information about the seizure onset zone and potentially serve as a broader biomarker for identifying these areas, beyond just the stimulated sites. We hypothesize that high-frequency (50 Hz) intracortical stimulation increases the number of interictal spikes at the SOZ.

The subsequent chapters of this study will sequentially outline a method chapter that comprehensively details all procedures, followed by a results chapter that presents the study's findings, and a discussion chapter that will explore the insights, interpretations, and significance of the study's outcomes.

Chapter 2

2 Methods

2.1 Patients

In this study, we recruited patients with drug-resistant epilepsy (18 years and older) who underwent invasive presurgical evaluation at the Epilepsy Monitoring Unit of the University Hospital, London Health Sciences Center. The study received approval from Western's Research Ethics Board, and all participants provided written informed consent before the examination.

Our dataset comprised 135 patients at the time of analysis, of which 108 underwent high-frequency cortical stimulation. Patients who received any form of neuromodulation—including deep brain stimulation, responsive neurostimulation, or vagus nerve stimulation —were excluded from the analysis. The final cohort included 26 patients who underwent resection and 4 patients who underwent ablation, all of whom became seizure-free following intervention (**Figure 1**). This selection ensured that the treated areas were the seizure onset zones.

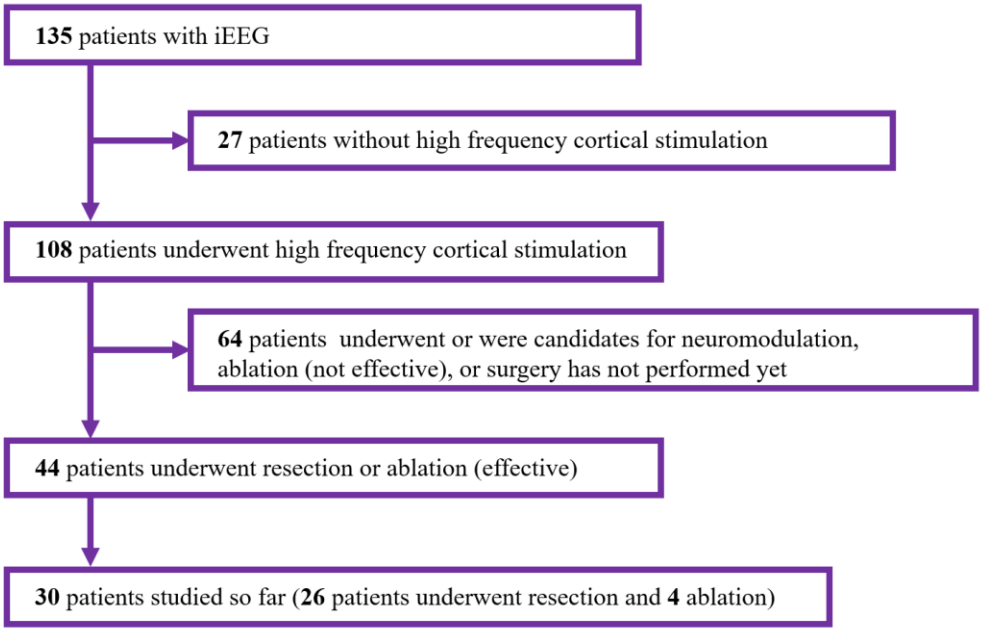


Figure 1. Patients' flowchart

A total of 30 patients (18 female; age range: 18-59 years; mean age = 31.36 years; standard deviation = 11.12) were analyzed in this study. Detailed patient information is summarized in **Table 1**.

2.2 Electrode implantation

SEEG is an invasive technique for monitoring EEG utilizing depth electrodes. These types of electrodes typically feature a diameter of 0.86 mm with platinum contacts, each 2.29 mm long. The number of contacts per electrode ranges from four to eighteen with an intercontact distance of three to six millimeters based on the electrode type. Before surgery, the placement of electrodes should be planned to target specific areas of the brain potentially involved in seizure initiation. Following implantation, the position of electrodes is typically confirmed through small burr holes using computed tomography co-registered with preoperative MRI (Marti et al., 2022).

Table 1. Patient profile

Nu	Age	Sex	Nu. of elect	Nu. Stim trial	Diagnosis	Pathology
1	31	F	10	11	Lt TLE	HS
2	23	F	8	17	Rt MTLE	NS
3	24	F	13	26	Lt TLE	RG
4	41	F	8	42	Lt MTLE	RG
5	24	M	11	36	Lt TLE	NO
6	28	M	9	21	Lt OLE/TLE	RG
7	20	M	10	59	Lt FLE/ TLE	MTS
8	24	F	12	8	Lt TLE	NO
9	28	M	7	11	Lt MTLE	NO
10	19	F	11	8	Lt TLE	MTS
11	32	F	12	29	Rt FLE	FCD
12	32	F	19	11	Rt MFLE	NO
13	33	F	8	24	Rt FLE	FCD
14	21	F	9	2	Rt MTLE	MTS
15	25	M	10	1	Rt TLE	RG
16	34	M	14	10	Rt TLE	NO
17	34	F	8	40	Rt TLE	HS
18	27	M	13	64	Lt FLE	NO
19	43	F	10	50	Rt TLE	RG
20	59	F	14	24	Rt TLE	NS
21	36	M	9	28	Rt FLE	NO
22	19	F	16	24	Lt ILE	NO
23	39	M	13	36	Lt OLE	FCD
24	27	F	8	6	Rt FLE	NS
25	20	M	8	10	Lt MTLE	NO
26	46	F	8	31	Rt MTLE	MTS
27	49	M	15	21	Rt FLE	NS
28	18	F	14	24	Lt MTLE	MTS
29	26	M	9	23	Lt MTLE	MTS
30	58	F	12	12	Rt TLE	MTS

Lt: Left, Rt: Right, TLE: Temporal lobe epilepsy, MTLE: Mesial temporal lobe epilepsy, OLE: Occipital lobe epilepsy, FLE: Frontal lobe epilepsy, HS: Hippocampal sclerosis, RG: Reactive gliosis, MTS: Mesial temporal sclerosis, ILE: Insular lobe epilepsy, FCD: Focal cortical dysplasia, NS: Nonspecific changes, NO: No information

2.3 Electrical Cortical Stimulation

Electrical stimulation should be conducted following the recording of interictal data and typical electroclinical seizures. During stimulation, a precise 3-dimensional map of the contacts concerning cortical topography and brain structures should be readily available. Patients should be well-rested and alert during the procedure. stimulation should be conducted for a total duration of 60 minutes, with the session not extending beyond 90 minutes to maintain the patient's thorough collaboration. Before stimulation, patients should be thoroughly briefed on the tasks they will need to complete during stimulation to ensure their full understanding. Stimulation is ideally performed in a spacious, quiet room equipped for recording audio and video throughout the entire stimulation session. It is important to establish a rational order of stimulation, upon a list of the channels to be stimulated is finalized. Contacts covering the potential SOZ should be reserved for the end of the stimulation session considering the potential occurrence of seizures. At our center, electrical stimuli were delivered using the Nicolet Cortical Stimulation device (Natus)®, a rectangular pulse generator with a constant current. Stimulation parameters typically range from 1 to 6 mA, with a pulse width of 250 to 500 μs, at 40 to 60 Hz (**Table 2**). Stimulation is applied at lower intensities for 1–3 seconds or till the clinical symptoms manifest(Marti et al., 2022).

Table 2. Stimulation parameters

Parameters for High Frequency	
Stimulation Mode	Bipolar
Stimulation Frequency	50 Hz
Current	1–6 mA
Stimulation Time	5 s
Interval InterStimulations	≥10 s
Pulse Width	300 μs

In this project, we exclusively analyzed high-frequency stimulation data. The stimulation conditions were consistent: 50 Hz, alternating square pulse of 0.3 ms duration, bipolar, current of 1–6 mA, for 5 seconds (**Figure 2**). These parameters were used to stimulate both the non-SOZ and SOZ. Stimulation began at 1 mA and intensity was incrementally increased until clinical symptoms appeared, after-discharges or seizures were triggered, or the maximum intensity was reached. The total duration of stimulation and the delivered charge were kept within established safety limits.

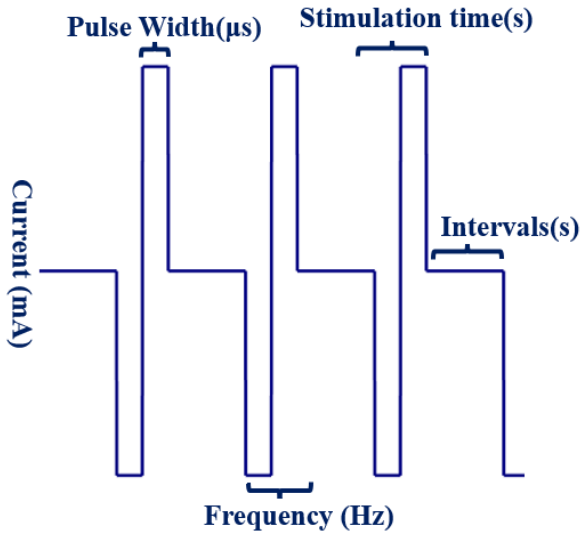


Figure 2. Biphasic stimulation mode

2.4 Preparing the data.

Intracranial recordings were sampled at 2048 Hz without applying a digital filter, and were collected at three stages: before, during, and after stimulation. Following data collection, electrode locations were verified through CT and MRI scans, and noisy channels were excluded to ensure data quality. For analysis, we used a bipolar derivation technique, subtracting consecutive channel signals, as stimulation was delivered in bipolar mode. The data was segmented into baseline (pre-stimulation) and post-stimulation periods (the signal segment following the application of maximum current over a pair of channels, as illustrated in **Figure 3**).

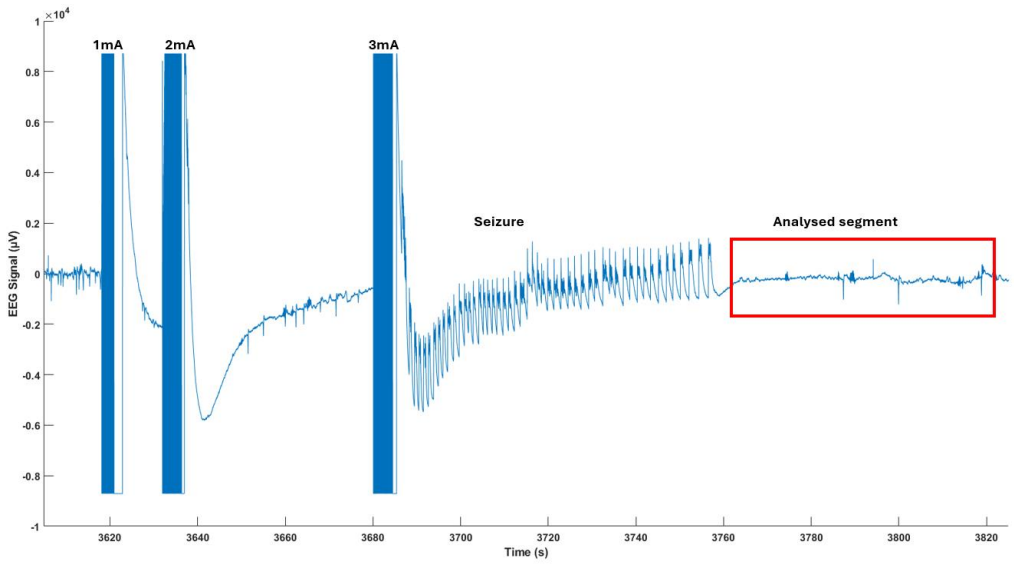


Figure 3. Analyzed segment.

Additionally, Notch biquad filters with a 4 Hz bandwidth were used to attenuate the 60 Hz hum noise. Visual inspection was conducted to identify and remove potential artifacts. From the cleaned signals, interictal epileptiform discharges were extracted. The preprocessing and interictal epileptiform discharge extraction steps are detailed in **Figure 4**.

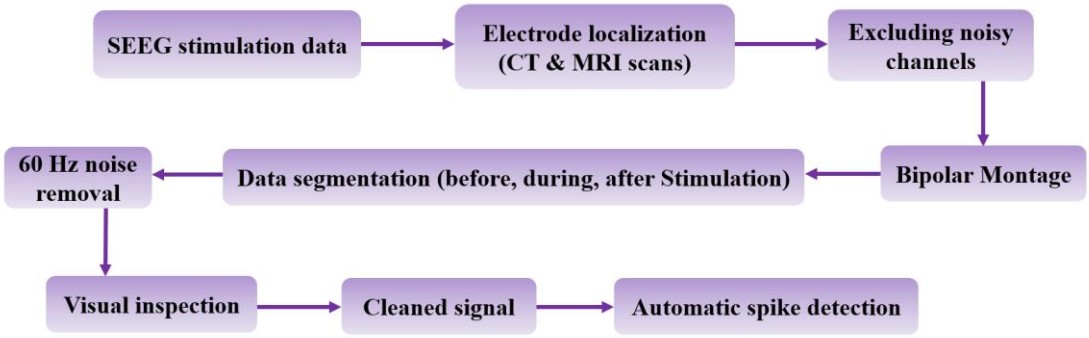


Figure 4. Preprocessing Pipeline

2.5 IED extraction

The visual analysis of multi-channel and long-term intracranial recordings is time-intensive and prone to biases. Consequently, robust techniques and algorithms for automatic IED detection have been developed in recent years. In our study, we utilized the IED detection algorithm developed by Janca(Janca et al., 2015). This IED detection algorithm adaptively models the statistical distributions of the signal envelopes and distinguishes signals encompassing IEDs from those representing background activity. In the frequency spectrum, IEDs are identified by a local increase in energy, particularly within the 14.3–50 Hz frequency range. Consequently, each contact underwent zero-phase filtering within a 10–60 Hz band using a combination of lowpass and high-pass Chebyshev digital filters (type II, 8th order) incorporating stopband ripple. All analysis was performed in MATLAB Rb2022. This detector outperforms a well-established detector and human readers. It also has the capability of detecting low-amplitude IEDs, which are typically overlooked by neurophysiologists and may provide a significant source of clinical insights. **Figure 5** shows examples of IEDs detected in the invasive EEG using the algorithm.

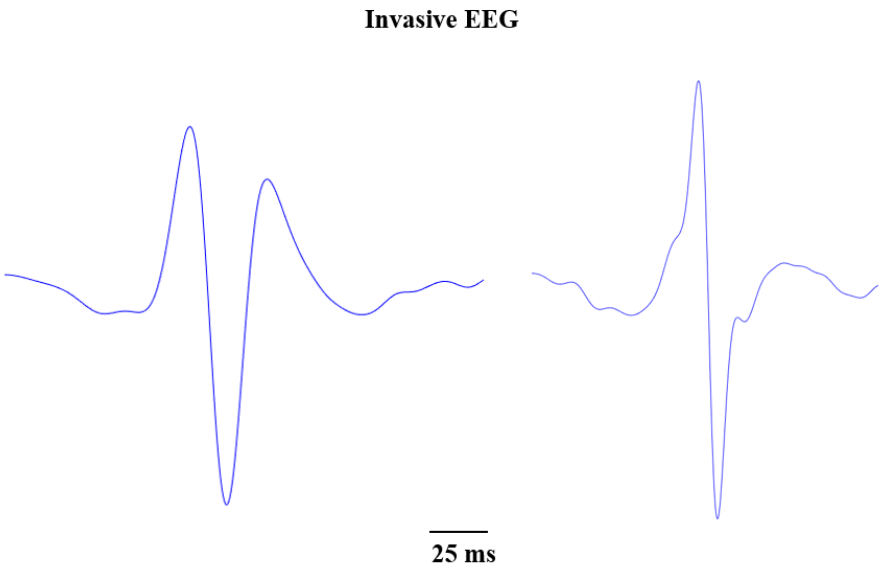


Figure 5. Samples of detected IEDs using the algorithm.

2.6 Optimizing SEEG analysis during stimulation: key considerations

Several factors should be taken into account when analyzing intracranial recordings. Firstly, SEEG recordings involve multiple electrodes, typically ranging from twelve to eighteen, with each electrode containing up to fifteen contacts (typically ten). Some contacts might record signals from the same IED generators. Consequently, bipolar channels with the highest concentration of IEDs are the primary generators of IEDs and other channels exhibit the propagation of IEDs (Köksal-Ersöz et al., 2022). Secondly, there is a growing body of evidence indicating that high-frequency cortical stimulation can lead to not only local but also remote activations (Barborica et al., 2022). In essence, high-frequency cortical stimulation delivered via SEEG primarily influences the targeted area, yet it can also impact neighboring and interconnected brain regions. The final aspect to consider is neural fragility, which measures the degree of imbalance among network nodes; Essentially, even minor impulse perturbations within the network can potentially trigger seizures. Within the epilepsy context, a fragile node necessitates a smaller perturbation to initiate seizure activity. Research has shown that neural fragility is higher (lower) in electrode contacts situated within clinically annotated SOZ for patients who experience a successful (unsuccessful) outcome (Li et al., 2021). This suggests that depending on the extent to which cortical stimulation affects the seizure onset zones, these regions may display greater epileptic activity compared to the directly stimulated sites. Hence, our investigation encompasses spike activity not only in the channels subjected to stimulation but also in all other non-stimulated contacts. To maintain consistency across all patient datasets, we computed the normalized absolute change in spike count. The spike rate change is determined by subtracting the spike rate before stimulation from the spike rate after stimulation. This normalized absolute change in spike count is then obtained by dividing the spike rate change by the maximum spike rate change.

2.7 Statistical analysis

The delineation of SOZ and non-SOZ regions was achieved by considering various examination results and a comprehensive clinical interpretation (interictal and ictal SEEG recordings). These identified areas were subsequently validated in the selected patient cohort (as detailed in **Table 1**), where individuals achieved seizure freedom post-treatment. Consequently, each contact within the intracranial electrode array was categorized based on this classification. Our analytical approach involved conducting two distinct analyses, one focusing on contacts directly subjected to stimulation and the other on those not influenced by stimulation. To assess differences between the SOZ and non-SOZ groups, we employed the Mann-Whitney U test ($p < 0.001$). Furthermore, we utilized the receiver operating characteristic (ROC) curve methodology to determine an optimal threshold value for the bimodal classifier, facilitating the classification of SOZ and non-SOZ regions.

Chapter 3

3 Results

Building upon the groundwork laid in the preceding chapters, Chapter 3 delves into the empirical outcomes of our investigation into high-frequency cortical stimulation for drug-resistant epilepsy.

3.1 Labeling contacts

Initially, SOZ and non-SOZ were determined through examination results and supplementary clinical interpretation (interictal and ictal SEEG recordings). These identifications were confirmed by the seizure-free outcomes of the patients after undergoing surgery or ablation.

3.2 Example patient

In this section, we provide a detailed description of a stimulation session and demonstrate how monitoring spike activity during stimulation can offer insight into SOZ localization. We discuss the results for a right-handed 58-year-old patient diagnosed with right temporal lobe epilepsy.

The patient was implanted with six pairs of electrodes targeting the left and right amygdala, insula, anterior hippocampus, posterior hippocampus, orbital frontal, and posterior cingulate (**Figure 6**).

Delivering stimulation over bipolar channels can cause different events depending on whether they are in the epileptogenic zone or the propagation zone. These events can include afterdischarges, electrical events such as subclinical EEG seizures, electroclinical events such as stimulation-induced seizures, and no stimulation-induced events (normal).

The patient underwent 12 stimulation trials across both hemispheres, starting with the least epileptic channels and progressing to the most epileptic ones as determined during pre-stimulation monitoring (**Table 3**).

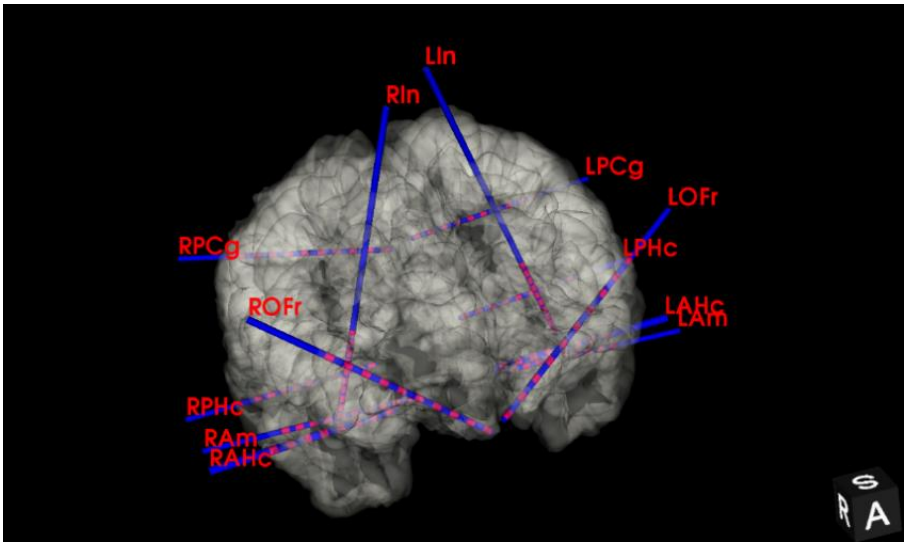


Figure 6. 3D view of depth electrode location in a patient. The depth electrodes in the left hemisphere covered: Amygdala (LAm), Anterior Hippocampus (LAHc), Posterior Hippocampus (LPHc), Insula (LIn), Orbital frontal cortex (LOFr), Posterior Cingulate (LPCg). The depth electrodes in the Right hemisphere covered: Amygdala (RAm), Anterior Hippocampus (RAHc), Posterior Hippocampus (RPHc), Insula (RIn), Orbital frontal cortex (ROFr), Posterior Cingulate (RPCg).

The bipolar stimulation trials were conducted over the following channels: left insula channels 1 and 2, left insula channels 3 and 4, left posterior hippocampus channels 1 and 2, left posterior hippocampus channels 3 and 4, left anterior hippocampus channels 1 and 2, left anterior hippocampus channels 3 and 4, right insula channels 1 and 2, right insula channels 3 and 4, right amygdala channels 1 and 2, right insula channels 2 and 3, right anterior hippocampus channels 1

and 2, and finally, right posterior hippocampus channels 1 and 2. The patient was diagnosed with right temporal lobe epilepsy. As shown in **Table 3**, stimulating the epileptogenic and seizure onset zones identified during intracranial monitoring led to the emergence of afterdischarges and seizures. The maximum current delivered was adjusted based on the responses observed after each stimulation trial.

Table 3. Stimulation trials

Trial	Channels	Current	Event
1	LIn 1-2	1-6 mA	Normal
2	LIn 3-4	1-6 mA	Normal
3	LPHc 1-2	1-6 mA	Normal
4	LPHc 3-4	1-6 mA	Normal
5	LAHc 1-2	1-6 mA	Afterdischarges
6	LAHc 3-4	1-6 mA	Normal
7	RIn 1-2	1-4 mA	Normal
8	RIn 3-4	1-4 mA	Afterdischarges
9	RAm 1-2	1-3 mA	Seizure
10	RIn 2-3	1-5 mA	Afterdischarges
11	RAHc 1-2	1-4 mA	Seizure
12	RPHc 1-2	1-4 mA	Afterdischarges

Considering all the factors discussed in section 2.6, the frequency of interictal epileptiform discharges was computed following each stimulation trial, with its pattern of occurrence across all channels depicted in **Figure 7**.

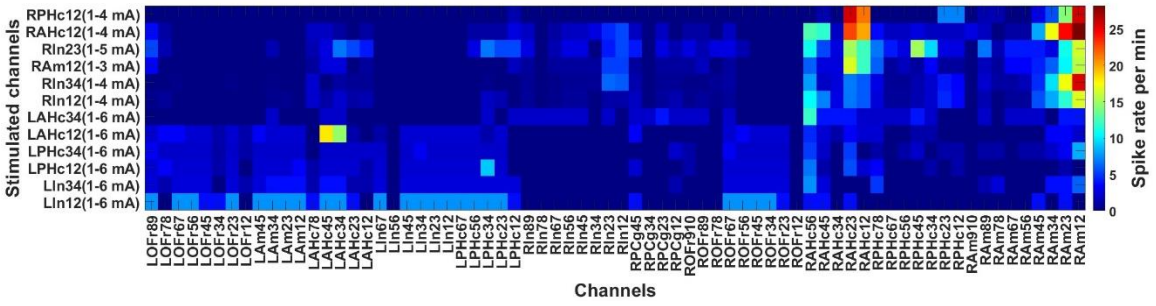


Figure 7. Spikes generation pattern over all channels after each stimulation trial

Figure 7 illustrates that stimulating the seizure onset zone results in a marked increase in spike activity. This elevated spike activity is also evident when adjacent areas to the SOZ are stimulated, both before and following direct SOZ stimulation. These findings suggest that the heightened excitability of the SOZ extends to neighboring regions, highlighting the interconnected nature of epileptic activity within the brain. Epileptic activity may fluctuate throughout the day; however, during stimulation sessions, each node is pushed to its maximum capacity for generating spike activity. Our approach is limited by the responses elicited after stimulation and the safety thresholds for the maximum current applied. By utilizing the cumulative number of interictal epileptiform discharges recorded after each stimulation trial, we constructed an epileptogenicity map of the brain (**Figure 8**). Using this epileptogenicity map, we can interpret the events occurring after each stimulation trial. Stimulation of regions that produced a lower number of IEDs did not trigger any events. In contrast, stimulation of areas with the highest IED counts during the session induced seizures and afterdischarges.

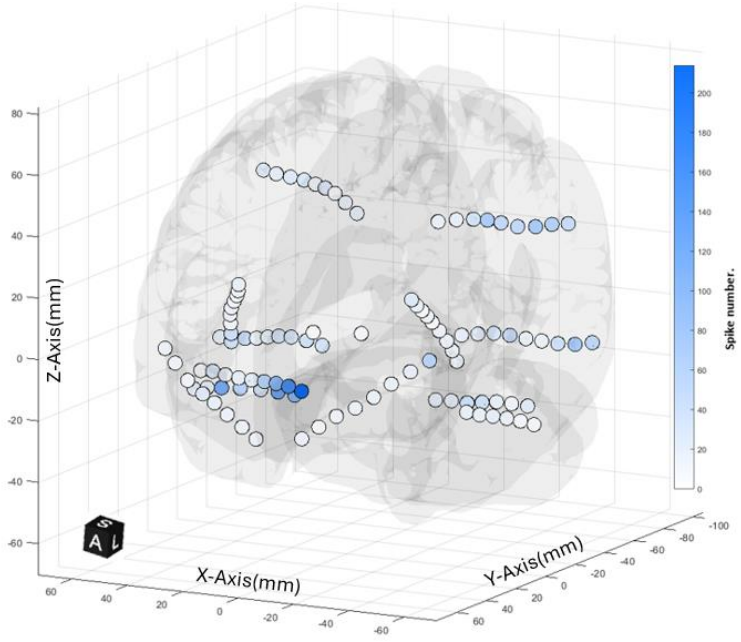


Figure 8. Epileptogenicity map based on the total number of spikes.

The epileptogenicity map of the patient can also be constructed using real MRI scans. In **Figure 9**, the solid segments indicate the areas monitored with depth electrodes. The dark blue regions correspond to the areas that evoked higher IEDs following stimulation.

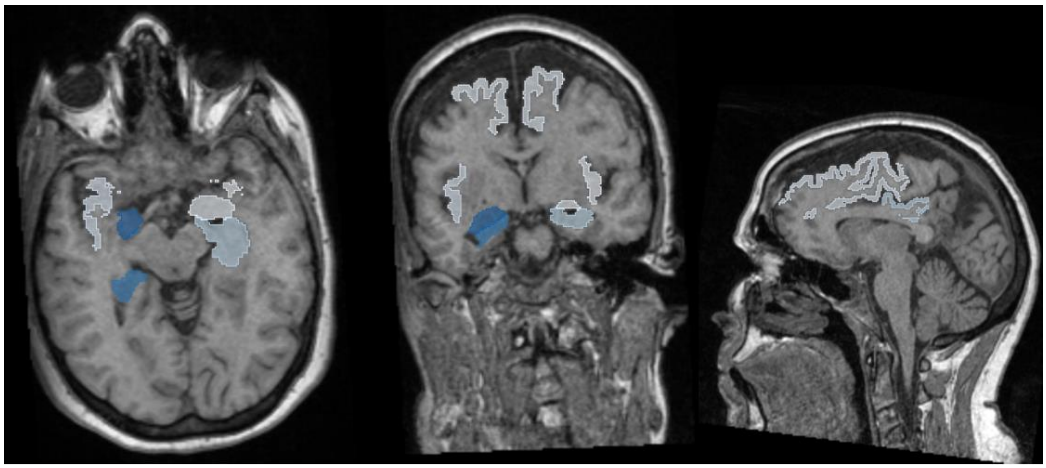


Figure 9. Epileptogenicity map on Patient's real MRI scan.
From left to right: the axial, coronal, and sagittal views.

In this patient, the right amygdala and hippocampus exhibited significant hyperexcitability, producing after-discharges and seizures. These findings indicate that the epileptogenic network involves the right mesial temporal region, including the amygdala and hippocampus, which also generated the highest number of IEDs during the stimulation session. Cortical stimulation activates neuronal tissues, and recordings of the brain's responses to these perturbations shed light on pathological connectivity and cortical excitability within the epileptic brain network(Frauscher et al., 2023a). The normal function of the brain arises from intricate interactions among interconnected brain regions. In the concept of epilepsy, these networks become disrupted, leading to seizures. Nodes with strong connections within these networks are frequently targeted for epilepsy surgery (Rijal et al., 2023). **Figure 10** represents epileptic connectivity across contacts for the example patient. the strength of connections in the connectivity map is determined by the spike rate values. Specifically, the spike rate values during stimulation are used to construct a connectivity matrix where each entry represents the strength of connectivity between two brain regions. The higher the spike rate value between two regions, the stronger the connection (mne circular connectivity graph). The suspicion is that areas with a higher degree of connectivity after stimulation are likely to be more epileptic and should be included in the resection.

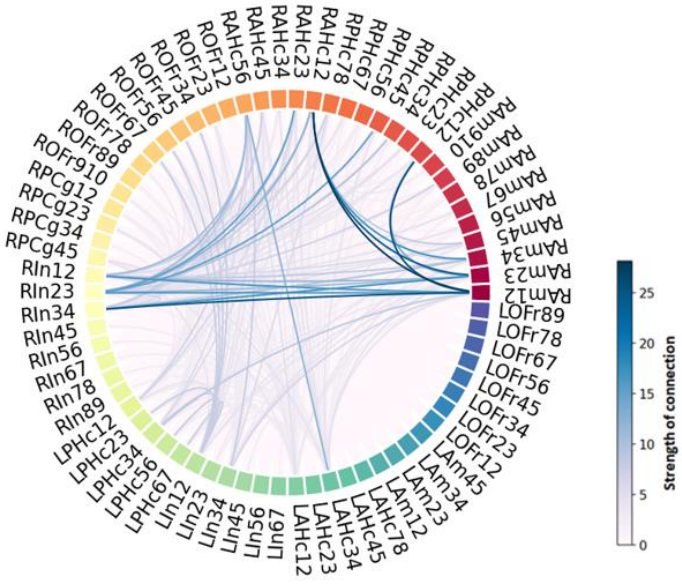


Figure 10. Connectivity matrix

3.3 Results over all patients

3.3.1 Effect of stimulation at the site of stimulation

To maintain consistency in results across all 30 patients, we calculated the normalized absolute change in spike counts for each contact point, both pre and post-stimulation. This method allowed us to standardize the data, ensuring reliable comparisons of spike activity changes across various patients and stimulation sites. As previously mentioned, these patients were seizure-free post-surgery, enabling us to delineate seizure onset zones and non-seizure onset zones based on clinical assessments and surgical outcomes. The change in spike counts at the stimulation sites is shown in **Figure 11**. The x-axis shows the normalized absolute change in spike activity, which is a measure of how much spike activity has changed relative to a baseline (it has been normalized to the highest change for each patient). The y-axis shows the population density of the recordings per value. Green bars represent changes in spikes at the SOZ after SOZ stimulation and the purple bars represent changes in spikes at non-SOZ regions after non-SOZ stimulation. The analysis demonstrated a statistically significant difference in spike changes between SOZ and non-SOZ regions, as indicated by the Mann-Whitney U test ($p < 0.001$). To develop our quantitative method for SOZ identification, we employed a receiver operating characteristic curve to determine an optimal threshold value for SOZ identification. The red dashed line indicates a threshold value, which is used to distinguish significant changes in spike activity. The high population density of the purple bar indicates that a significant number of non-SOZ regions experienced minimal changes in spike activity following stimulation. Specificity of 0.97, indicating a high true negative rate and sensitivity of 0.94, indicating a high true positive rate. Area under the curve of 0.98, suggesting excellent discrimination between SOZ and non-SOZ based on spike changes. This suggests that non-SOZ areas typically have less excitability or response to stimulation compared to SOZ regions, which aligns with the expected behavior where SOZ regions are more responsive to stimulation due to their epileptogenic nature. The threshold line helps differentiate significant changes, and the data show that most non-SOZ changes fall below this threshold.

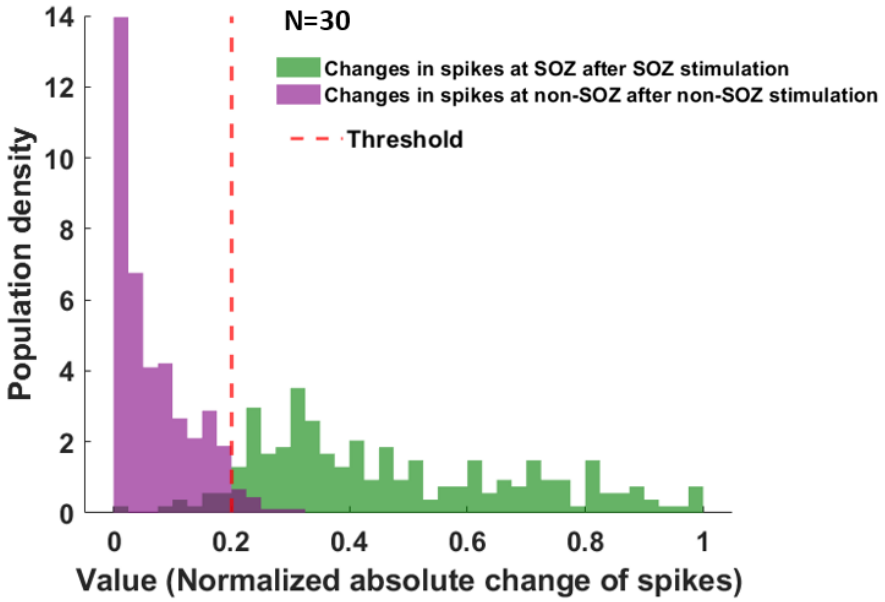


Figure 11. The effect of stimulation at the SOZ and non-SOZ (site of stimulation). A significant difference between the two groups (Mann-Whitney U test, p-value <0.001). Threshold value: 0.2 (ROC). Specificity: 0.97. Sensitivity: 0.94. AUC: 0.98.

3.3.2 Effect of stimulation at non-stimulated areas

Figure 12 presents the changes in spike counts in non-stimulated areas (refer to the appendix for alternative presentations that offer clearer distinctions). The analysis indicates a significant difference in spike changes between SOZ and non-SOZ regions (Mann-Whitney U test, p-value < 0.001). Similar to the stimulation site analysis, we utilized a receiver operating characteristic curve to establish a threshold for SOZ identification. To improve the specificity and sensitivity of the bimodal classifier in our study, we focused on the highest change evoked at each contact following stimulation, rather than examining all recordings in non-stimulated regions. **Figure 13** shows the highest change at each contact in the areas that were not stimulated.

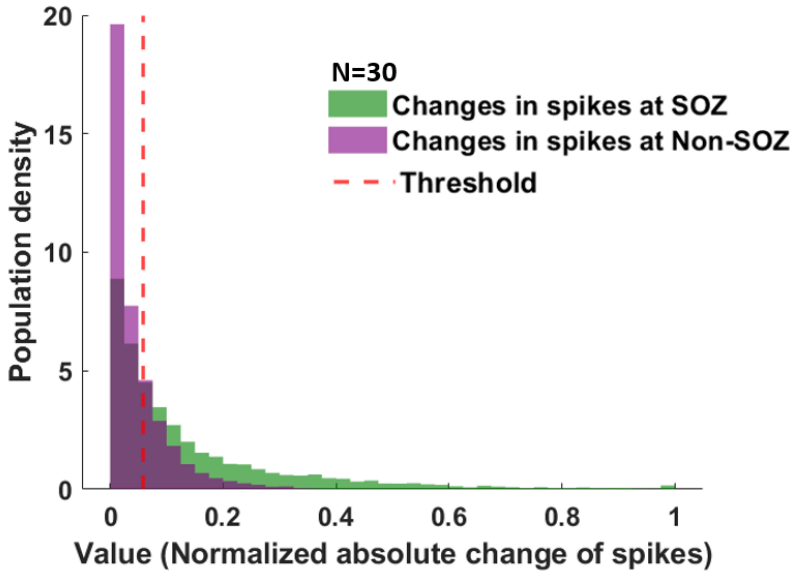


Figure 12. The effect of stimulation at non-stimulated areas.

A significant difference between the two groups (Mann-Whitney U test, p-value <0.001).

Threshold value: 0.05 (ROC). Specificity: 0.73. Sensitivity: 0.57. AUC: 0.71.

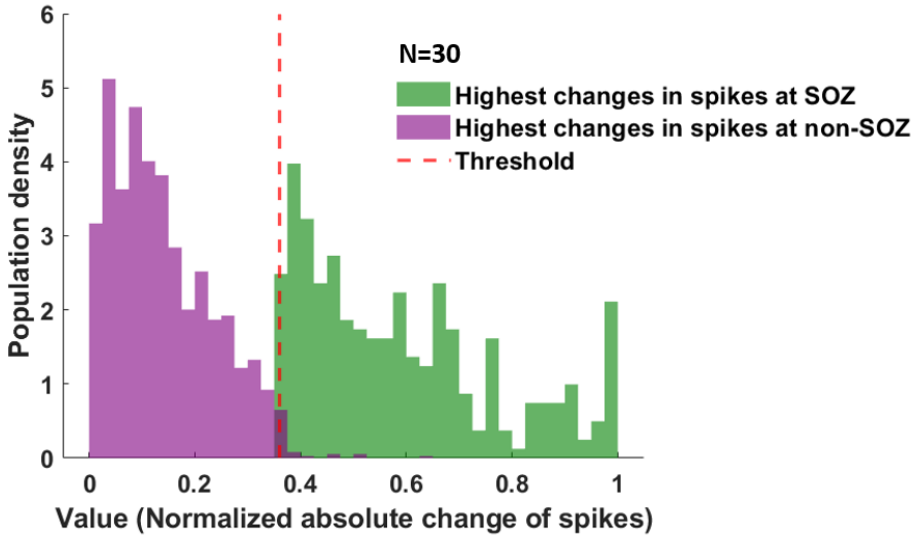


Figure 13. The effect of stimulation at non-stimulated areas (highest changes).

A significant difference between the two groups (Mann-Whitney U test, p-value <0.001).

Threshold value: 0.36 (ROC). Specificity: 0.98. Sensitivity: 1. AUC: 0.99.

The results indicate an increase in the number of IEDs at the SOZ, even in regions that were not directly stimulated. This demonstrates that the effect of stimulation extends beyond the immediate site of stimulation. These findings suggest that stimulation-induced spikes can emerge as a biomarker for identifying seizure onset zones.

Chapter 4

4 Discussion

Epilepsy, a chronic neurological disorder marked by recurrent seizures, presents significant challenges to both individuals and healthcare systems worldwide (R. S. Fisher et al., 2005). Despite advancements in pharmacological treatments, a substantial proportion of patients continue to experience drug-resistant seizures, highlighting the need for alternative therapeutic strategies. Surgical interventions targeting the seizure onset zone have become a promising option for drug-resistant epilepsy patients. This study investigated the effect of 50 Hz stimulation on IEDs during extra-operative intracortical stimulation, aimed to enhance the accuracy of SOZ localization. More specifically, the effect of stimulation both at the site of stimulation and non-stimulated areas was studied to monitor connectivity patterns across individual patients, localizing activated regions following stimulation. An in-depth analysis of individual patients provided valuable insights into the dynamic interplay within the epileptogenic networks. By selectively targeting specific brain regions, distinct patterns of epileptic activity were elicited. Response variability across patients underscored the heterogeneity of epileptogenic networks and highlighted the importance of personalized treatment approaches in epilepsy management. Our study revealed a significant change in interictal epileptiform discharges at the SOZ following stimulation, even in regions not directly stimulated. This stimulation-induced spike activity emerged as a reliable biomarker for identifying epileptogenic zones, offering valuable insights into the underlying pathophysiology of

drug-resistant epilepsy. Quantitative analysis of spike changes at stimulation sites and non-stimulated areas elucidated a clear distinction between SOZ and non-SOZ regions. These quantitative insights provide a robust framework for guiding surgical interventions in drug-resistant epilepsy patients, ultimately leading to improved seizure management and quality of life.

The observed increase in the number of interictal epileptiform discharges following cortical stimulation can be attributed to several underlying mechanisms. Stimulation induces depolarization of neurons in proximity to the stimulation sites, leading to an increased likelihood of synchronous firing. This phenomenon, known as depolarization block, results from the accumulation of sodium ions within neurons, causing a transient suppression of neuronal activity followed by a period of hyperexcitability. Furthermore, CS may alter the balance of excitatory and inhibitory neurotransmission, potentially leading to an overall increase in neuronal excitability within the stimulated region.

The differential response of channels in epileptogenic and non-epileptogenic zones to CS underscores the underlying pathophysiological distinctions between these regions. In epileptogenic zones, the neural circuitry is characterized by a lower threshold for synchronized neuronal firing, likely due to an imbalance between excitatory and inhibitory inputs. CS may disrupt this delicate balance, leading to an increase in IED frequency. Conversely, in non-epileptogenic zones, the inhibitory mechanisms are more effective in suppressing abnormal neuronal firing, resulting in a comparatively muted response to CS (Kobayashi et al., 2021).

The study's findings align with the existing body of literature that highlights the intricate interplay between neural network modulation and IED generation. It is well-established that IEDs arise from the aberrant synchronization of neuronal populations, often driven by local excitatory-inhibitory imbalances. CS, acting as an external perturbation, further modulates this delicate network, potentially exacerbating the generation and propagation of IEDs. The observed increase in IEDs following CS in the channels where seizures were triggered provides empirical evidence of this phenomenon.

Our study provides valuable insights into the clinical utility of cortical stimulation for probing excitation in epilepsy. Nevertheless, in most conditions, stimulation techniques have been

utilized to inhibit epileptic seizures. Due to the paradoxical association of excessive or increased activity of interneuron and synchronized GABA-mediated inhibitory postsynaptic potentials with seizure generation, the reciprocal impacts of cortical stimulation can be elucidated by considering the degree to which GABA-mediated modulation is involved(Nakatani et al., 2020).

4.1 Limitations and Future Directions

Our methodological framework included patient recruitment from a specialized epilepsy center, coupled with stringent inclusion criteria, ensuring a homogeneous sample with well-defined clinical characteristics. The utilization of intracranial multiple contact electrodes enabled precise recording of brain activity during stimulation sessions, facilitating detailed analysis of stimulation-induced changes in epileptic networks. Standardized stimulation parameters and protocols ensured consistency across patients, enhancing the reliability and reproducibility of our findings. However, despite these promising findings, our study is not without limitations. The results may have limited generalizability due to the study's single-site design and the relatively small number of patients included. Future studies with larger cohorts and multi-center collaborations are warranted to validate the findings and further elucidate the role of stimulation on IEDs in SOZ localization. A long-term follow-up study is necessary to assess the durability of surgical outcomes and the risk of seizure recurrence.

Additionally, the number of electrodes implanted, and the implantation areas varied across patients, as did the stimulation areas. This inconsistency prevented us from performing a structure-based analysis applicable to all patients. Furthermore, the pathology of epilepsy can influence biomarkers in intracranial electroencephalography data. The specific characteristics and patterns of epileptic activity detected in SEEG can differ based on the underlying pathology causing the epilepsy. Our cohort included patients with diverse pathologies and epilepsy types, which introduces variability in our findings. Therefore, future studies with larger sample sizes focusing on each specific pathology and epilepsy type are necessary to validate and extend our results.

4.2 Significance

Our results, derived from a single session of stimulation, revealed information comparable to that obtained from intracranial monitoring conducted over several days, as well as from other established modalities for SOZ identification. This finding underscores the critical importance of data gleaned from stimulation sessions. Such efficiency not only reduces the time required for effective diagnosis but also minimizes the risks and discomforts associated with prolonged invasive monitoring.

The ability to rely on stimulation-based information is particularly vital in scenarios where ictal activity does not occur during presurgical monitoring. Additionally, it becomes crucial when prolonged patient hospitalization is infeasible due to infection risks or other medical complications. In such cases, the efficiency of single-session stimulation in providing critical diagnostic information ensures that patients receive timely and accurate evaluations without the need for extended and potentially hazardous monitoring periods.

From another perspective, controlled stimulation sessions facilitate the study of connected neural pathways via tracking generation and propagation patterns of stimulation-induced IEDs, enabling the identification of fragile and highly interconnected nodes. This capability is pivotal for advancing our understanding of neural network dynamics and pathophysiology.

In certain instances, it is challenging to evoke patients' typical seizures due to specific limitations of the patient’s condition. Consequently, stimulation may need to be limited to language mapping while avoiding areas that might evoke seizures. Therefore, monitoring the effect of stimulation on interictal phenomena can be critical.

4.3 Conclusions

In summary, this research illustrated the excitatory effects of the high-frequency intracortical stimulation at the seizure onset zones, evidenced by an increase in the number of IEDs, which suggests that stimulation-induced spikes can be used as a biomarker to identify the SOZ. The study

indicates that stimulation via SEEG can potentially evoke cortical excitability, enhancing excitation while decreasing inhibition. These findings suggest that tracking changes in IEDs post-stimulation may help in identifying the optimal stimulation parameters in therapies for DRE patients. Our study underscores the transformative potential of high-frequency cortical stimulation in the management of drug-resistant epilepsy, leading to personalized and tailored treatment strategies and subsequently improved patient outcomes. By leveraging advanced neurophysiological techniques and computational approaches, we can unravel the complex dynamics of epileptogenic networks and develop targeted interventions tailored to each patient's unique pathophysiology.

References

Aaronson, D. M., Martinez Del Campo, E., Boerger, T. F., Conway, B., Cornell, S., Tate, M., Mueller, W. M., Chang, E. F., & Krucoff, M. O. (2021). Understanding Variable Motor Responses to Direct Electrical Stimulation of the Human Motor Cortex During Brain Surgery. In *Frontiers in Surgery* (Vol. 8). Frontiers Media S.A. https://doi.org/10.3389/fsurg.2021.730367

Alcala-Zermeno, J. L., Starnes, K., Gregg, N. M., Worrell, G., & Lundstrom, B. N. (2023). Responsive neurostimulation with low-frequency stimulation. *Epilepsia*, *64*(2), e16–e22. https://doi.org/10.1111/epi.17467

Arcot Desai, S., Tcheng, T. K., & Morrell, M. J. (2019). Quantitative electrocorticographic biomarkers of clinical outcomes in mesial temporal lobe epileptic patients treated with the RNS® system. *Clinical Neurophysiology*, *130*(8), 1364–1374. https://doi.org/10.1016/j.clinph.2019.05.017

Barborica, A., Oane, I., Donos, C., Daneasa, A., Mihai, F., Pistol, C., Dabu, A., Roceanu, A., & Mindruta, I. (2022). Imaging the effective networks associated with cortical function through intracranial high-frequency stimulation. *Human Brain Mapping*, *43*(5), 1657–1675. https://doi.org/10.1002/hbm.25749

Basic Mechanisms Underlying Seizures and Epilepsy. (n.d.). http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/epilepsy/basicores4.ppt

Baumgartner, C., Koren, J. P., Britto-Arias, M., Zoche, L., & Pirker, S. (2019). Presurgical epilepsy evaluation and epilepsy surgery [version 1; peer review: 2 approved]. In *F1000Research* (Vol. 8). F1000 Research Ltd. https://doi.org/10.12688/f1000research.17714.1

Brown, M. W., Porter, B. E., Dlugos, D. J., Keating, J., Gardner, A. B., Storm, P. B., & Marsh, E. D. (2007). Comparison of novel computer detectors and human performance for spike detection in intracranial EEG. *Clinical Neurophysiology*, *118*(8), 1744–1752. https://doi.org/10.1016/j.clinph.2007.04.017

Chassoux, F., Devaux, B., Landré, E., Turak, B., Nataf, F., Varlet, P., Chodkiewicz, J.-P., & Daumas-Duport, C. (2000). Stereoelectroencephalography in focal cortical dysplasia A 3D approach to delineating the dysplastic cortex. In *Brain* (Vol. 123).

Chiang, S., Khambhati, A. N., Wang, E. T., Vannucci, M., Chang, E. F., & Rao, V. R. (2021). Evidence of state-dependence in the effectiveness of responsive neurostimulation for seizure modulation. *Brain Stimulation*, *14*(2), 366–375. https://doi.org/10.1016/j.brs.2021.01.023

Chvojka, J., Kudlacek, J., Chang, W. C., Novak, O., Tomaska, F., Otahal, J., Jefferys, J. G. R., & Jiruska, P. (2021). The role of interictal discharges in ictogenesis — A dynamical perspective. In *Epilepsy and Behavior* (Vol. 121). Academic Press Inc. https://doi.org/10.1016/j.yebeh.2019.106591

Cuello Oderiz, C., Von Ellenrieder, N., Dubeau, F., Eisenberg, A., Gotman, J., Hall, J., Hincapié, A. S., Hoffmann, D., Job, A. S., Khoo, H. M., Minotti, L., Olivier, A., Kahane, P., & Frauscher, B. (2019). Association of Cortical Stimulation-Induced Seizure with Surgical Outcome in Patients with Focal Drug-Resistant Epilepsy. *JAMA Neurology*, *76*(9), 1070–1078. https://doi.org/10.1001/jamaneurol.2019.1464

De Curtis, M., Jefferys, J. G. R., & Avoli, M. (2012). *Interictal Epileptiform Discharges in Partial Epilepsy Complex Neurobiological Mechanisms Based on Experimental and Clinical Evidence*. https://www.ncbi.nlm.nih.gov/books/

Engel, J., Pitkanen, A., Loeb, J. A., Dudek, F. E., Bertram, E. H., Cole, A. J., Moshé, S. L., Wiebe, S., Jensen, F. E., Mody, I., Nehlig, A., & Vezzani, A. (2013). Epilepsy biomarkers. *Epilepsia*, *54*(SUPPL.4), 61–69. https://doi.org/10.1111/epi.12299

Englot, D. J., Rolston, J. D., Wright, C. W., Hassnain, K. H., & Chang, E. F. (2016). Rates and Predictors of Seizure Freedom with Vagus Nerve Stimulation for Intractable Epilepsy. *Neurosurgery*, *79*(3), 345–353. https://doi.org/10.1227/NEU.0000000000001165

epileptogenic zone. (n.d.).

Ersoz, E. K., Modolo, J., Bartolomei, F., & Wendling, F. (2020). Neural mass modeling of slow-fast dynamics of seizure initiation and abortion. *PLoS Computational Biology*, *16*(11). https://doi.org/10.1371/journal.pcbi.1008430

Ezzyat, Y., & Suthana, N. (n.d.). *Brain Stimulation*.

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M., Hesdorffer, D. C., Lee, B. I., Mathern, G. W., Moshé, S. L., Perucca, E., Scheffer, I. E., Tomson, T., Watanabe, M., & Wiebe, S. (2014). ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550

Fisher, R. S., Van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. (2005). Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). In *Epilepsia* (Vol. 46, Issue 4, pp. 470–472). https://doi.org/10.1111/j.0013-9580.2005.66104.x

Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., … Young, C. (2010). Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*, *51*(5), 899–908. https://doi.org/10.1111/j.1528-1167.2010.02536.x

Frauscher, B., Bartolomei, F., Baud, M. O., Smith, R. J., Worrell, G., & Lundstrom, B. N. (2023a). Stimulation to probe, excite, and inhibit the epileptic brain. *Epilepsia*, *64*(S3), S49–S61. https://doi.org/10.1111/epi.17640

Frauscher, B., Bartolomei, F., Baud, M. O., Smith, R. J., Worrell, G., & Lundstrom, B. N. (2023b). Stimulation to probe, excite, and inhibit the epileptic brain. *Epilepsia*. https://doi.org/10.1111/epi.17640

Gonzalez-Martinez, J., Bulacio, J., Alexopoulos, A., Jehi, L., Bingaman, W., & Najm, I. (2013). Stereoelectroencephalography in the “difficult to localize” refractory focal epilepsy: Early experience from a North American epilepsy center. *Epilepsia*, *54*(2), 323–330. https://doi.org/10.1111/j.1528-1167.2012.03672.x

Gordon a-c, B., Lesser a-d, R. P., Rance, N. E., Hart, J., Webber, R., Uematsu, S., & Fisher, R. S. (1990). *Parameters for direct cortical electrical stimulation in the human: histopathologic confirmation* (Vol. 75).

Guery, D., & Rheims, S. (2021). Clinical management of drug resistant epilepsy: A review on current strategies. In *Neuropsychiatric Disease and Treatment* (Vol. 17, pp. 2229–2242). Dove Medical Press Ltd. https://doi.org/10.2147/NDT.S256699

Hofer, K. T., Kandrács, Á., Tóth, K., Hajnal, B., Bokodi, V., Tóth, E. Z., Erőss, L., Entz, L., Bagó, A. G., Fabó, D., Ulbert, I., & Wittner, L. (2022). Bursting of excitatory cells is linked to interictal epileptic discharge generation in humans. *Scientific Reports*, *12*(1). https://doi.org/10.1038/s41598-022-10319-4

Janca, R., Jezdik, P., Cmejla, R., Tomasek, M., Worrell, G. A., Stead, M., Wagenaar, J., Jefferys, J. G. R., Krsek, P., Komarek, V., Jiruska, P., & Marusic, P. (2015). Detection of Interictal Epileptiform Discharges Using Signal Envelope Distribution Modelling: Application to Epileptic and Non-Epileptic Intracranial Recordings. *Brain Topography*, *28*(1), 172–183. https://doi.org/10.1007/s10548-014-0379-1

Jobst, B. C., Darcey, T. M., Thadani, V. M., & Roberts, D. W. (2010). Brain stimulation for the treatment of epilepsy. *Epilepsia*, *51*(SUPPL. 3), 88–92. https://doi.org/10.1111/j.1528-1167.2010.02618.x

Kassie J. Bollig, D. L. J. (2018). Seizures in Pregnancy. *Obstetrics and Gynecology Clinics of North America*, *45*(2), 349–367.

Kinoshita, M., Ikeda, A., Matsuhashi, M., Matsumoto, R., Hitomi, T., Begum, T., Usui, K., Takayama, M., Mikuni, N., Miyamoto, S., Hashimoto, N., & Shibasaki, H. (2005). Electric cortical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. *Clinical Neurophysiology*, *116*(6), 1291–1299. https://doi.org/10.1016/j.clinph.2005.02.010

Kinoshita, M., Ikeda, A., Matsumoto, R., Begum, T., Usui, K., Yamamoto, J., Matsuhashi, M., Takayama, M., Mikuni, N., Takahashi, J., Miyamoto, S., & Shibasaki, H. (2004). Electric stimulation on human cortex suppresses fast cortical activity and epileptic spikes. *Epilepsia*, *45*(7), 787–791. https://doi.org/10.1111/j.0013-9580.2004.60203.x

Kobayashi, K., Matsumoto, R., Usami, K., Matsuhashi, M., Shimotake, A., Kikuchi, T., Yoshida, K., Kunieda, T., Miyamoto, S., Takahashi, R., & Ikeda, A. (2021). Cortico-cortical evoked potential by

single-pulse electrical stimulation is a generally safe procedure. *Clinical Neurophysiology*, *132*(5), 1033–1040. https://doi.org/10.1016/j.clinph.2020.12.022

Köksal-Ersöz, E., Lazazzera, R., Yochum, M., Merlet, I., Makhalova, J., Mercadal, B., Sanchez-Todo, R., Ruffini, G., Bartolomei, F., Benquet, P., & Wendling, F. (2022). Signal processing and computational modeling for interpretation of SEEG-recorded interictal epileptiform discharges in epileptogenic and non-epileptogenic zones. *Journal of Neural Engineering*, *19*(5). https://doi.org/10.1088/1741-2552/ac8fb4

Kovac, S., Kahane, P., & Diehl, B. (2016). Seizures induced by direct electrical cortical stimulation - Mechanisms and clinical considerations. In *Clinical Neurophysiology* (Vol. 127, Issue 1, pp. 31–39). Elsevier Ireland Ltd. https://doi.org/10.1016/j.clinph.2014.12.009

Li, A., Huynh, C., Fitzgerald, Z., Cajigas, I., Brusko, D., Jagid, J., Claudio, A. O., Kanner, A. M., Hopp, J., Chen, S., Haagensen, J., Johnson, E., Anderson, W., Crone, N., Inati, S., Zaghloul, K. A., Bulacio, J., Gonzalez-Martinez, J., & Sarma, S. V. (2021). Neural fragility as an EEG marker of the seizure onset zone. *Nature Neuroscience*, *24*(10), 1465–1474. https://doi.org/10.1038/s41593-021-00901-w

Lopes, M. A., Junges, L., Woldman, W., Goodfellow, M., & Terry, J. R. (2020). The Role of Excitability and Network Structure in the Emergence of Focal and Generalized Seizures. *Frontiers in Neurology*, *11*. https://doi.org/10.3389/fneur.2020.00074

Lundstrom, B. N., Gompel, J. Van, Khadjevand, F., Worrell, G., & Stead, M. (2019). Chronic subthreshold cortical stimulation and stimulation-related EEG biomarkers for focal epilepsy. *Brain Communications*, *1*(1). https://doi.org/10.1093/braincomms/fcz010

Makhalova, J., Madec, T., Medina Villalon, S., Jegou, A., Lagarde, S., Carron, R., Scavarda, D., Garnier, E., Bénar, C. G., & Bartolomei, F. (2023). The role of quantitative markers in surgical prognostication after stereoelectroencephalography. *Annals of Clinical and Translational Neurology*, *10*(11), 2114–2126. https://doi.org/10.1002/acn3.51900

Marti, A. S., Mirsattari, S. M., Steven, D. A., McLachlan, R. S., Parrent, A. G., Hayman-Abello, S., MacDougall, K. W., Andrade, A., de Ribaupierre, S., Diosy, D. C., & Burneo, J. G. (2022). Extraoperative electrical stimulation mapping in epilepsy presurgical evaluation: a proposal and

review of the literature. *Clinical Neurology and Neurosurgery*, *214*. https://doi.org/10.1016/j.clineuro.2022.107170

Matsumoto, R., Kunieda, T., & Nair, D. (2017). Single pulse electrical stimulation to probe functional and pathological connectivity in epilepsy. In *Seizure* (Vol. 44, pp. 27–36). W.B. Saunders Ltd. https://doi.org/10.1016/j.seizure.2016.11.003

Matsumoto, R., Nair, D. R., LaPresto, E., Bingaman, W., Shibasaki, H., & Lüders, H. O. (2007). Functional connectivity in human cortical motor system: A cortico-cortical evoked potential study. *Brain*, *130*(1), 181–197. https://doi.org/10.1093/brain/awl257

Matsumoto, R., Nair, D. R., LaPresto, E., Najm, I., Bingaman, W., Shibasaki, H., & Lüders, H. O. (2004). Functional connectivity in the human language system: A cortico-cortical evoked potential study. *Brain*, *127*(10), 2316–2330. https://doi.org/10.1093/brain/awh246

Maturana, M. I., Meisel, C., Dell, K., Karoly, P. J., D'Souza, W., Grayden, D. B., Burkitt, A. N., Jiruska, P., Kudlacek, J., Hlinka, J., Cook, M. J., Kuhlmann, L., & Freestone, D. R. (2020). Critical slowing down as a biomarker for seizure susceptibility. *Nature Communications*, *11*(1). https://doi.org/10.1038/s41467-020-15908-3

Morrell, M. J. (2011). *Responsive cortical stimulation for the treatment of medically intractable partial epilepsy On behalf of the RNS System in Epilepsy Study Group*. https://www.neurology.org

Munari, C., Kahane, P., TassP, L., Francione, S., Hoffmann, D., Lo Russo, G., & Benabid, A. L. (1993a). Intracerebral Low Frequency Electrical Stimulation: a New Tool for the Definition of the "Epileptogenic Area"? In *Acta Neurochir* (Vol. 58).

Munari, C., Kahane, P., TassP, L., Francione, S., Hoffmann, D., Lo Russo, G., & Benabid, A. L. (1993b). Intracerebral Low Frequency Electrical Stimulation: a New Tool for the Definition of the "Epileptogenic Area"? In *Acta Neurochir* (Vol. 58).

Nair, D. R., Morrell, M. J., Skarpaas, T. L., Murro, A. M., Park, Y. D., Barkley, G. L., Smith, B. J., Gwinn, R. P., Doherty, M. J., Noe, K. H., Zimmerman, R. S., Bergey, G. K., Anderson, W. S., Heck, C., Liu, C. Y., Lee, R. W., Sadler, T., Duckrow, R. B., Hirsch, L. J., … Skarpaas, T. L. (2020). Nine-year prospective

efficacy and safety of brain-responsive neurostimulation for focal epilepsy. *Neurology*, *95*(9), E1244–E1256. https://doi.org/10.1212/WNL.0000000000010154

Nakatani, M., Matsumoto, R., Kobayashi, K., Hitomi, T., Inouchi, M., Matsuhashi, M., Kinoshita, M., Kikuchi, T., Yoshida, K., Kunieda, T., Miyamoto, S., Takahashi, R., Hattori, N., & Ikeda, A. (2020). Electrical cortical stimulations modulate spike and post-spike slow-related high-frequency activities in human epileptic foci. *Clinical Neurophysiology*, *131*(8), 1741–1754. https://doi.org/10.1016/j.clinph.2020.03.042

Neumann, A. R., Raedt, R., Steenland, H. W., Sprengers, M., Bzymek, K., Navratilova, Z., Mesina, L., Xie, J., Lapointe, V., Kloosterman, F., Vonck, K., Boon, P. A. J. M., Soltesz, I., Mcnaughton, B. L., & Luczak, A. (n.d.). *Involvement of fast-spiking cells in ictal sequences during spontaneous seizures in rats with chronic temporal lobe epilepsy Abbreviations: KA = kainic acid injection model; LFP = local field potential; PP = perforant path stimulation model; TLE = temporal lobe epilepsy*. https://doi.org/10.1093/awx205

NONLINEAR DYNAMICS AND CHAOS. (n.d.).

Prime, D., Rowlands, D., O'Keefe, S., & Dionisio, S. (2018). Considerations in performing and analyzing the responses of cortico-cortical evoked potentials in stereo-EEG. In *Epilepsia* (Vol. 59, Issue 1, pp. 16–26). Blackwell Publishing Inc. https://doi.org/10.1111/epi.13939

Rijal, S., Corona, L., Perry, M. S., Tamilia, E., Madsen, J. R., Stone, S. S. D., Bolton, J., Pearl, P. L., & Papadelis, C. (2023). Functional connectivity discriminates epileptogenic states and predicts surgical outcome in children with drug resistant epilepsy. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-36551-0

Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. In *Brain* (Vol. 124).

Russo, S., Mikulan, E., Zauli, F. M., Sartori, I., Solbiati, M., Furregoni, G., Porro, M., Revay, M., Rosanova, M., David, O., Massimini, M., Tassi, L., & Pigorini, A. (2023). Neocortical and medial temporal seizures have distinct impacts on brain responsiveness. *Epilepsia*, *64*(6), e118–e126. https://doi.org/10.1111/epi.17580

Ryvlin, P., Rheims, S., Hirsch, L. J., Sokolov, A., & Jehi, L. (2021). Neuromodulation in epilepsy: state-of-the-art approved therapies. In *The Lancet Neurology* (Vol. 20, Issue 12, pp. 1038–1047). Elsevier Ltd. https://doi.org/10.1016/S1474-4422(21)00300-8

Saggio, M. L., Crisp, D., Scott, J. M., Karoly, P., Kuhlmann, L., Nakatani, M., Murai, T., Dümpelmann, M., Schulze-Bonhage, A., Ikeda, A., Cook, M., Gliske, S. V., Lin, J., Bernard, C., Jirsa, V., & Stacey, W. C. (2020). A taxonomy of seizure dynamotypes. *ELife*, *9*, 1–56. https://doi.org/10.7554/eLife.55632

Salanova, V., Sperling, M. R., Gross, R. E., Irwin, C. P., Vollhaber, J. A., Giftakis, J. E., & Fisher, R. S. (2021). The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. *Epilepsia*, *62*(6), 1306–1317. https://doi.org/10.1111/epi.16895

Samanta, D. (2022). Recent developments in stereo electroencephalography monitoring for epilepsy surgery. In *Epilepsy and Behavior* (Vol. 135). Academic Press Inc. https://doi.org/10.1016/j.yebeh.2022.108914

Schroeder, G. M., Chowdhury, F. A., Cook, M. J., Diehl, B., Duncan, J. S., Karoly, P. J., Taylor, P. N., & Wang, Y. (2022). Multiple mechanisms shape the relationship between pathway and duration of focal seizures. *Brain Communications*, *4*(4). https://doi.org/10.1093/braincomms/fcac173

Simpson, H. D., Schulze-Bonhage, A., Cascino, G. D., Fisher, R. S., Jobst, B. C., Sperling, M. R., & Lundstrom, B. N. (2022). Practical considerations in epilepsy neurostimulation. In *Epilepsia* (Vol. 63, Issue 10, pp. 2445–2460). John Wiley and Sons Inc. https://doi.org/10.1111/epi.17329

Smith, E. H., Liou, J. Y., Merricks, E. M., Davis, T. S., Thomson, K., Greger, B., House, P. A., Emerson, R. G., Goodman, R. R., McKhann, G. M., Sheth, S. A., Schevon, C. A., & Rolston, J. D. (2022). Title: Human interictal epileptiform discharges are bidirectional traveling waves echoing ictal discharges. *ELife*, *11*. https://doi.org/10.7554/eLife.73541

Smith, G., & Stacey, W. C. (2021). The accuracy of quantitative EEG biomarker algorithms depends upon seizure onset dynamics. *Epilepsy Research*, *176*. https://doi.org/10.1016/j.eplepsyres.2021.106702

Smith, R. J., Hays, M. A., Kamali, G., Coogan, C., Crone, N. E., Kang, J. Y., & Sarma, S. V. (2022). Stimulating native seizures with neural resonance: A new approach to localize the seizure onset zone. *Brain*, *145*(11), 3886–3900. https://doi.org/10.1093/brain/awac214

Sobayo, T., & Mogul, D. J. (2016). Should stimulation parameters be individualized to stop seizures: Evidence in support of this approach. *Epilepsia*, *57*(1), 131–140. https://doi.org/10.1111/epi.13259

Staba, R. J., Stead, M., & Worrell, G. A. (2014). Electrophysiological Biomarkers of Epilepsy. In *Neurotherapeutics* (Vol. 11, Issue 2, pp. 334–346). Springer Science and Business Media, LLC. https://doi.org/10.1007/s13311-014-0259-0

Stead, M., Bower, M., Brinkmann, B. H., Lee, K., Marsh, W. R., Meyer, F. B., Litt, B., Van Gompel, J., & Worrell, G. A. (2010). Microseizures and the spatiotemporal scales of human partial epilepsy. *Brain*, *133*(9), 2789–2797. https://doi.org/10.1093/brain/awq190

Trébuchon, A., & Chauvel, P. (2016). Electrical Stimulation for Seizure Induction and Functional Mapping in Stereoelectroencephalography. In *Journal of Clinical Neurophysiology* (Vol. 33, Issue 6, pp. 511–521). Lippincott Williams and Wilkins. https://doi.org/10.1097/WNP.0000000000000313

Trebuchon, A., Racila, R., Cardinale, F., Lagarde, S., McGonigal, A., Lo Russo, G., Scavarda, D., Carron, R., Mai, R., Chauvel, P., Bartolomei, F., & Francione, S. (2021). Electrical stimulation for seizure induction during SEEG exploration: A useful predictor of postoperative seizure recurrence? *Journal of Neurology, Neurosurgery and Psychiatry*, *92*(1), 22–26. https://doi.org/10.1136/jnnp-2019-322469

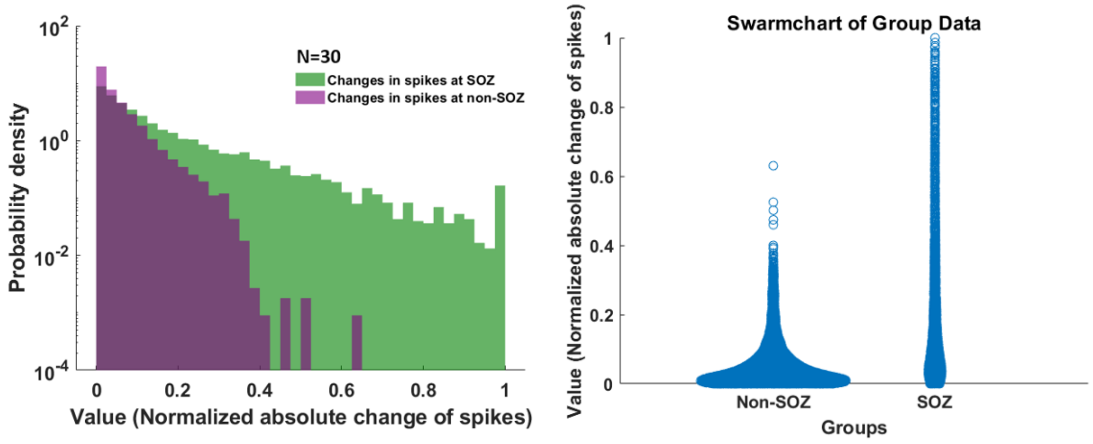
Truccolo, W., Donoghue, J. A., Hochberg, L. R., Eskandar, E. N., Madsen, J. R., Anderson, W. S., Brown, E. N., Halgren, E., & Cash, S. S. (2011). Single-neuron dynamics in human focal epilepsy. *Nature Neuroscience*, *14*(5), 635–643. https://doi.org/10.1038/nn.2782

van Klink, N., Frauscher, B., Zijlmans, M., & Gotman, J. (2016). Relationships between interictal epileptic spikes and ripples in surface EEG. *Clinical Neurophysiology*, *127*(1), 143–149. https://doi.org/10.1016/j.clinph.2015.04.059

Wilkat, T., Rings, T., & Lehnertz, K. (2019). No evidence for critical slowing down prior to human epileptic seizures. *Chaos*, *29*(9). https://doi.org/10.1063/1.5122759

Appendix

Appendix A: Alternative presentations of Figure 12.



a. Logarithmic presentation **b.** Swarm-chart presentation

A. logarithmic and b. swarm-chart presentations of **Figure 12** manifesting the clear distinction between SOZ and non-SOZ.

Curriculum Vitae

Ahdyie Ahmadi

Education:

• Master of Science in Neuroscience **2022-2024**
• Schulich School of Medicine & Dentistry, Western University, London, Canada
• Thesis: The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges
• Supervisors: Dr. Julio Martinez Trujillo, Dr. Ana Suller Marti

• Master of Science in Biomedical Engineering **2014-2017**
• Tarbiat Modares University, Tehran, Iran
• Thesis: EEG-based emotion recognition for wearable devices
• Supervisor: Dr. Seyed Mohammad Firoozabadi

• Bachelor of Science in Electrical Engineering **2009-2014**
• Babol Noshirvani University of Technology, Babol, Iran

Honours and Awards:

• Received the **Neuroscience travel scholarship** from Western University. **2023**

• Received **Western Graduate Research Scholarship** from Western University. **2022**

• Received a **full tuition waiver** from Tarbiat Modares University. **2014**

• Ranked within the **top 3%** among 30000 participants in the Iranian University Entrance Exam for a master's degree in the field of Biomedical Engineering. **2014**

• Received a **full tuition waiver** from Babol Noshirvani University of Technology. **2009**

• Ranked within the **top 0.7%** among 273668 participants in the Iranian University Entrance Exam in the field of Mathematics and Physics. **2009**

Presentations (Poster):

A. Ahmadi, et al., The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges,
poster at the American Epilepsy Society (**AES**), Orlando, USA (**2023**).

A. Ahmadi, et al., The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges,
poster at the Canadian League Against Epilepsy (**CLAE**) - Charlottetown, Prince Edward Island, Canada (**2023**).(**Neuroscience fall travel award, $500**)

A. Ahmadi, et al., The Effect of Cortical Stimulation on Interictal phenomena,
poster at the Southern Ontario Neuroscience Association (**SONA**), University of Toronto Scarborough, Canada (**2023**).

A. Ahmadi, et al., The Effect of Cortical Stimulation on Interictal Epileptiform Discharges (Case report), a poster at the Clinical Neurological Sciences (**CNS**) Research Day of Schulich School of Medicine & Dentistry, King's University College, Canada (**2023**).

A. Ahmadi, et al., EEG-based Emotion Recognition for Wearable Devices,
poster at the 4th Iranian Conference on Bioelectromagnetics (**ICBEM 2018**), Tarbiat Modares University, Tehran, Iran.

Presentations (Oral):

A. Ahmadi, et al., The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges, Canadian Epilepsy Research Initiative (**CERI**) Charlottetown, Prince Edward Island, Canada (**2023**).

A. Ahmadi, et al., The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges,
Western Epilepsy Research Day (**WERD**), Western University (**2024**).

A. Ahmadi, et al., The Effect of High-Frequency Cortical Stimulation on SEEG-recorded Interictal Epileptiform Discharges,
Oral Presentation at the Neuroscience Research Day (**NRD**), Western University (**2024**).

Work experience:

- Expert and Assistant of the Academic Affairs Office **2018-2020**
- Expert and Assistant of the Interdisciplinary Departments **2018-2020**
  Faculty of Interdisciplinary Sciences and Technologies, Tarbiat Modares University, Tehran, Iran

- Researcher, Neurochallange Company, Tehran, Iran **2017-2018**